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TITLE

Alpha-Ketoamide Inhibitors of Hepatitis C Virus NS3  
Protease

FIELD OF THE INVENTION

10 The present invention relates generally to a novel  
class of alpha-ketoamides which are useful as serine  
protease inhibitors, and more particularly as Hepatitis C  
virus NS3 protease inhibitors. This invention also relates  
to pharmaceutical compositions comprising these compounds  
and methods of using the same.

15

BACKGROUND OF THE INVENTION

Hepatitis C virus (HCV) is the major cause of  
transfusion and community-acquired non-A, non-B hepatitis  
worldwide. Approximately 2% of the world's population are  
infected with the virus. In the United States, hepatitis C  
20 represents approximately 20% of cases of acute hepatitis.  
Unfortunately, self-limited hepatitis is not the most  
common course of acute HCV infection. In the majority of  
patients, symptoms of acute hepatitis resolve, but alanine  
aminotransferase (a liver enzyme diagnostic for liver  
25 damage) levels often remain elevated and HCV RNA persists.  
Indeed, a propensity to chronicity is the most  
distinguishing characteristic of hepatitis C, occurring in  
at least 85% of patients with acute HCV infection. The  
factors that lead to chronicity in hepatitis C are not well  
30 defined. Chronic HCV infection is associated with  
increased incidence of liver cirrhosis and liver cancer.  
No vaccines are available for this virus, and current  
treatment is restricted to the use of alpha interferon,  
which is effective in only 15-20% of patients. Recent  
35 clinical studies have shown that combination therapy of  
alpha interferon and ribavirin leads to sustained efficacy  
in 40% of patients (Poynard, T. et al. *Lancet* **1998**, 352,  
1426-1432.). However, a majority of patients still either  
fail to respond or relapse after completion of therapy.

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## APPLICATION INFORMATION

Title Line One:: ALPHA-KETOAMIDE INHIBITORS OF HEPATITIS  
Title Line Two:: C VIRUS NS3 PROTEASE  
Total Drawing Sheets:: 0  
Formal Drawings?: No  
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## REPRESENTATIVE INFORMATION

Representative Customer Number:: 24348  
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## CONTINUITY INFORMATION

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5 Thus, there is a clear need to develop more effective  
therapeutics for treatment of HCV-associated hepatitis.

HCV is a positive-stranded RNA virus. Based on  
comparison of deduced amino acid sequence and the extensive  
similarity in the 5' untranslated region, HCV has been  
10 classified as a separate genus in the Flaviviridae family,  
which also includes flaviviruses such as yellow fever virus  
and animal pestiviruses like bovine viral diarrhea virus  
and swine fever virus. All members of the Flaviviridae  
family have enveloped virions that contain a positive  
15 stranded RNA genome encoding all known virus-specific  
proteins via translation of a single, uninterrupted, open  
reading frame.

Considerable heterogeneity is found within the  
nucleotide and encoded amino acid sequence throughout the  
20 HCV genome. At least six major genotypes have been  
characterized, and more than 50 subtypes have been  
described. The major genotypes of HCV differ in their  
distribution worldwide, and the clinical significance of  
the genetic heterogeneity of HCV remains elusive despite  
25 numerous studies of the possible effect of genotypes on  
pathogenesis and therapy.

The RNA genome is about 9.6 Kb in length, and encodes  
a single polypeptide of about 3000 amino acids. The 5'  
untranslated region contains an internal ribosome entry  
30 site (IRES), which directs cellular ribosomes to the  
correct AUG for initiation of translation. As was  
determined by transient expression of cloned HCV cDNAs, the  
precursor protein is cotranslationally and  
posttranslationally processed into at least 10 viral  
35 structural and nonstructural (NS) proteins by the action of  
a host signal peptidase and by two distinct viral  
proteinase activities. The translated product contains the  
following proteins: core-E1-E2-p7-NS2-NS3-NS4A-NS4B-NS5A-  
NS5B.

40 The N-terminal portion of NS3 functions as a  
proteolytic enzyme that is responsible for the cleavage of  
sites liberating the nonstructural proteins NS4A, NS4B,

5 NS5A, and NS5B. NS3 has further been shown to be a serine  
protease. Although the functions of the NS proteins are  
not completely defined, it is known that NS4A is a protease  
cofactor and NS5B is an RNA polymerase involved in viral  
10 processing of the viral polyprotein are expected to have  
antiviral activity.

There are several patents which disclose HCV NS3  
protease inhibitors. WO98/17679 describes peptide and  
peptidomimetic inhibitors with the following formula: U-E<sup>8</sup>-  
15 E<sup>7</sup>-E<sup>6</sup>-E<sup>5</sup>-E<sup>4</sup>-NH-CH(CH<sub>2</sub>G<sup>1</sup>)-W<sup>1</sup>, where W is one of a variety of  
electrophilic groups, including boronic acid or ester. E<sup>4</sup>  
represents either an amino acid or one of a series of  
peptidomimetic groups, the synthesis of which are not  
exemplified. HCV protease inhibitors described in the  
20 present case are not covered.

Based on the large number of persons currently  
infected with HCV and the limited treatments available, it  
is desirable to discover new inhibitors of HCV NS3  
protease.

25

#### SUMMARY OF THE INVENTION

Accordingly, one object of the present invention is to  
provide novel HCV NS3 protease inhibitors.

It is another object of the present invention to  
30 provide a novel method of treating HCV infection which  
comprises administering to a host in need of such treatment  
a therapeutically effective amount of at least one of the  
compounds of the present invention or a pharmaceutically  
acceptable salt form thereof.

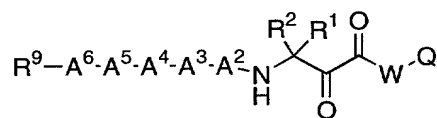
35 It is another object of the present invention to  
provide pharmaceutical compositions with HCV NS3 protease  
inhibiting activity comprising a pharmaceutically  
acceptable carrier and a therapeutically effective amount  
of at least one of the compounds of the present invention  
40 or a pharmaceutically acceptable salt form thereof.

5 It is another object of the present invention to provide a method of inhibiting HCV present in a body fluid sample which comprises treating the body fluid sample with an effective amount of a compound of the present invention. It is another object of the present invention to provide a  
 10 kit or container containing at least one of the compounds of the present invention in an amount effective for use as a standard or reagent in a test or assay for determining the ability of a potential pharmaceutical to inhibit HCV NS3 protease, HCV growth, or both.

15 It is another object of the present invention to provide novel compounds for use in therapy.

It is another object of the present invention to provide the use of novel compounds for the manufacture of a medicament for the treatment of HCV.

20 These and other objects, which will become apparent during the following detailed description, have been achieved by the inventors' discovery that compounds of Formula (I):



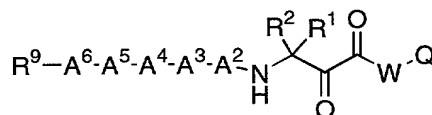
25 (I)

wherein W, Q, R<sup>1</sup>, R<sup>2</sup>, A<sup>2</sup>, A<sup>3</sup>, A<sup>4</sup>, A<sup>5</sup>, A<sup>6</sup>, and R<sup>9</sup>, are defined below, stereoisomeric forms, mixtures of stereoisomeric forms, or pharmaceutically acceptable salt  
 30 forms thereof, are effective HCV NS3 protease inhibitors.

#### DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[1] Thus, in a first embodiment, the present invention provides a novel compound of Formula I:

35



(I)

5

or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

W is -NH- or -O-;

10

Q is selected from:  $-(CR^{10}R^{10c})_n-Q^1$ ,  $-(CR^{10}R^{10c})_n-Q^2$ ,  
C<sub>1</sub>-C<sub>4</sub> alkyl substituted with Q<sup>1</sup>,  
C<sub>2</sub>-C<sub>4</sub> alkenyl substituted with Q<sup>1</sup>,  
C<sub>2</sub>-C<sub>4</sub> alkynyl substituted with Q<sup>1</sup>, and  
15 an amino acid residue;

Q<sup>1</sup> is selected from:

-CO<sub>2</sub>R<sup>11</sup>, -SO<sub>2</sub>R<sup>11</sup>, -SO<sub>3</sub>R<sup>11</sup>, -P(O)<sub>2</sub>R<sup>11</sup>, -P(O)<sub>3</sub>R<sup>11</sup>,  
aryl substituted with 0-4 Q<sup>1a</sup>, and  
20 5-6 membered heterocyclic group consisting of carbon  
atoms and 1-4 heteroatoms selected from the group:  
O, S, and N, said heterocyclic group substituted  
with 0-4 Q<sup>1a</sup>;

25 Q<sup>1a</sup> is H, F, Cl, Br, I, -NO<sub>2</sub>, -CN, -NCS, -CF<sub>3</sub>, -OCF<sub>3</sub>, -CH<sub>3</sub>,  
-OCH<sub>3</sub>, -CO<sub>2</sub>R<sup>19</sup>, -C(=O)NR<sup>19</sup>R<sup>19</sup>, -NHC(=O)R<sup>19</sup>, -SO<sub>2</sub>R<sup>19</sup>,  
-SO<sub>2</sub>NR<sup>19</sup>R<sup>19</sup>, -NR<sup>19</sup>R<sup>19</sup>, -OR<sup>19</sup>, -SR<sup>19</sup>, C<sub>1</sub>-C<sub>4</sub> alkyl,  
C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkyl, or C<sub>1</sub>-C<sub>4</sub> haloalkoxy;

30 R<sup>19</sup> is C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, aryl, aryl(C<sub>1</sub>-C<sub>4</sub>  
alkyl), C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or C<sub>3</sub>-C<sub>6</sub> cycloalkyl(C<sub>1</sub>-C<sub>4</sub>  
alkyl);

alternatively, NR<sup>19</sup>R<sup>19</sup> may form a 5-6 membered heterocyclic  
35 group consisting of carbon atoms, a nitrogen atom, and  
optionally a second heteroatom selected from the group:  
O, S, and N;

R<sup>10</sup> is selected from the group: -CO<sub>2</sub>R<sup>11</sup>, -NR<sup>11</sup>R<sup>11</sup>, and C<sub>1</sub>-C<sub>6</sub>  
40 alkyl substituted with 0-1 R<sup>10a</sup>;

5

R<sup>10a</sup> is selected from the group: halo, -NO<sub>2</sub>, -CN, -CF<sub>3</sub>,  
-CO<sub>2</sub>R<sup>11</sup>, -NR<sup>11</sup>R<sup>11</sup>, -OR<sup>11</sup>, -SR<sup>11</sup>, -C(=NH)NH<sub>2</sub>, and aryl  
substituted with 0-1 R<sup>10b</sup>;

10 R<sup>10b</sup> is selected from the group: -CO<sub>2</sub>H, -NH<sub>2</sub>, -OH, -SH, and  
-C(=NH)NH<sub>2</sub>;

R<sup>10c</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

15 alternatively, R<sup>10</sup> and R<sup>10c</sup> can be combined to form a C<sub>3</sub>-C<sub>6</sub>  
cycloalkyl group substituted with 0-1 R<sup>10a</sup>;

R<sup>11</sup> is, at each occurrence, independently H or C<sub>1</sub>-C<sub>4</sub> alkyl;

20 R<sup>11a</sup> is H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl,  
C<sub>2</sub>-C<sub>4</sub> alkynyl, aryl, aryl(C<sub>1</sub>-C<sub>4</sub> alkyl)-,  
C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or C<sub>3</sub>-C<sub>6</sub> cycloalkyl(C<sub>1</sub>-C<sub>4</sub> alkyl)-;

Q<sup>2</sup> is -X-NR<sup>12</sup>-Z, -NR<sup>12</sup>-Y-Z, or -X-NR<sup>12</sup>-Y-Z;

25

X is selected from the group: -C(=O)-, -S-, -S(=O)-,  
-S(=O)<sub>2</sub>-, -P(O)-, -P(O)<sub>2</sub>-, and -P(O)<sub>3</sub>-;

Y is selected from the group: -C(=O)-, -S-, -S(=O)-,  
30 -S(=O)<sub>2</sub>-, -P(O)-, -P(O)<sub>2</sub>-, and -P(O)<sub>3</sub>-;

R<sup>12</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

Z is C<sub>1</sub>-C<sub>4</sub> haloalkyl,

35 C<sub>1</sub>-C<sub>4</sub> alkyl substituted with 0-3 Z<sup>a</sup>,  
C<sub>2</sub>-C<sub>4</sub> alkenyl substituted with 0-3 Z<sup>a</sup>,  
C<sub>2</sub>-C<sub>4</sub> alkynyl substituted with 0-3 Z<sup>a</sup>,  
C<sub>3</sub>-C<sub>10</sub> cycloalkyl substituted with 0-5 Z<sup>b</sup>,  
C<sub>3</sub>-C<sub>10</sub> carbocycle substituted with 0-5 Z<sup>b</sup>,

5 aryl substituted with 0-5 Z<sup>b</sup>,  
5-10 membered heterocyclic group consisting of carbon  
atoms and 1-4 heteroatoms selected from the group:  
O, S, and N, said heterocyclic group substituted  
with 0-4 Z<sup>b</sup>;  
10 an amino acid residue, or  
-A<sup>7</sup>-A<sup>8</sup>-A<sup>9</sup>;

Z<sup>a</sup> is H, F, Cl, Br, I, -NO<sub>2</sub>, -CN, -NCS, -CF<sub>3</sub>, -OCF<sub>3</sub>,  
-CH<sub>3</sub>, -OCH<sub>3</sub>, -CO<sub>2</sub>R<sup>20</sup>, -C(=O)NR<sup>20</sup>R<sup>20</sup>, -NHC(=O)R<sup>20</sup>,  
15 -NR<sup>20</sup>R<sup>20</sup>, -OR<sup>20</sup>, -SR<sup>20</sup>, -S(=O)R<sup>20</sup>, -SO<sub>2</sub>R<sup>20</sup>, -SO<sub>2</sub>NR<sup>20</sup>R<sup>20</sup>,  
C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkyl,  
C<sub>1</sub>-C<sub>4</sub> haloalkoxy,

C<sub>3</sub>-C<sub>10</sub> cycloalkyl substituted with 0-5 Z<sup>b</sup>,  
20 C<sub>3</sub>-C<sub>10</sub> carbocycle substituted with 0-5 Z<sup>b</sup>,  
aryl substituted with 0-5 Z<sup>b</sup>, or  
5-10 membered heterocyclic group consisting of carbon  
atoms and 1-4 heteroatoms selected from the group:  
O, S, and N, said heterocyclic group substituted  
25 with 0-4 Z<sup>b</sup>;

Z<sup>b</sup> is H, F, Cl, Br, I, -NO<sub>2</sub>, -CN, -NCS, -CF<sub>3</sub>, -OCF<sub>3</sub>,  
-CH<sub>3</sub>, -OCH<sub>3</sub>, -CO<sub>2</sub>R<sup>20</sup>, -C(=O)NR<sup>20</sup>R<sup>20</sup>, -NHC(=O)R<sup>20</sup>,  
-NR<sup>20</sup>R<sup>20</sup>, -OR<sup>20</sup>, -SR<sup>20</sup>, -S(=O)R<sup>20</sup>, -SO<sub>2</sub>R<sup>20</sup>, -SO<sub>2</sub>NR<sup>20</sup>R<sup>20</sup>,  
30 C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkyl,  
C<sub>1</sub>-C<sub>4</sub> haloalkoxy,

C<sub>3</sub>-C<sub>10</sub> cycloalkyl substituted with 0-5 Z<sup>c</sup>,  
C<sub>3</sub>-C<sub>10</sub> carbocycle substituted with 0-5 Z<sup>c</sup>,  
35 aryl substituted with 0-5 Z<sup>c</sup>, or  
5-10 membered heterocyclic group consisting of carbon  
atoms and 1-4 heteroatoms selected from the group:  
O, S, and N, said heterocyclic group substituted  
with 0-4 Z<sup>c</sup>;



5

$Z^C$  is H, F, Cl, Br, I,  $-NO_2$ ,  $-CN$ ,  $-NCS$ ,  $-CF_3$ ,  $-OCF_3$ ,  
 $-CH_3$ ,  $-OCH_3$ ,  $-CO_2R^{20}$ ,  $-C(=O)NR^{20}R^{20}$ ,  $-NHC(=O)R^{20}$ ,  
 $-NR^{20}R^{20}$ ,  $-OR^{20}$ ,  $-SR^{20}$ ,  $-S(=O)R^{20}$ ,  $-SO_2R^{20}$ ,  $-SO_2NR^{20}R^{20}$ ,  
 $C_1-C_4$  alkyl,  $C_1-C_4$  alkoxy,  $C_1-C_4$  haloalkyl, or  $C_1-C_4$   
haloalkoxy;

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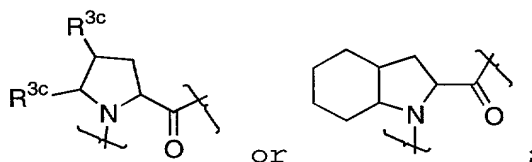
$R^{20}$  is H,  $C_1-C_4$  alkyl,  $C_1-C_4$  haloalkyl, aryl,  
aryl( $C_1-C_4$  alkyl)-,  $C_3-C_6$  cycloalkyl, or  
 $C_3-C_6$  cycloalkyl( $C_1-C_4$  alkyl)-;

15

alternatively,  $NR^{20}R^{20}$  may form a 5-6 membered heterocyclic  
group consisting of carbon atoms, a nitrogen atom, and  
optionally a second heteroatom selected from the  
group: O, S, and N;

20

$A^2$  is a bond,  $-NH-CR^3R^4-C(=O)-$ , an amino acid residue,



$A^3$  is a bond,  $-NH-CR^5R^6-C(=O)-$ , or an amino acid residue;

25

$A^4$  is a bond,  $-NH-CR^7R^8-C(=O)-$ , or an amino acid residue;

$A^5$  is a bond or an amino acid residue;

30  $A^6$  is a bond or an amino acid residue;

$A^7$  is a bond or an amino acid residue;

$A^8$  is an amino acid residue;

35

$A^9$  is an amino acid residue;

5 R<sup>1</sup> is selected from the group: H, F,  
C<sub>1</sub>-C<sub>6</sub> alkyl substituted with 0-3 R<sup>1a</sup>,  
C<sub>2</sub>-C<sub>6</sub> alkenyl substituted with 0-3 R<sup>1a</sup>,  
C<sub>2</sub>-C<sub>6</sub> alkynyl substituted with 0-3 R<sup>1a</sup>,  
aryl substituted with 0-5 R<sup>1a</sup>, and  
10 C<sub>3</sub>-C<sub>6</sub> cycloalkyl substituted with 0-3 R<sup>1a</sup>;

R<sup>1a</sup> is selected at each occurrence from the group:  
Cl, F, Br, I, CF<sub>3</sub>, CHF<sub>2</sub>, OH, =O, SH, -CO<sub>2</sub>R<sup>1b</sup>, -SO<sub>2</sub>R<sup>1b</sup>,  
-SO<sub>3</sub>R<sup>1b</sup>, -P(O)<sub>2</sub>R<sup>1b</sup>, -P(O)<sub>3</sub>R<sup>1b</sup>, -C(=O)NHR<sup>1b</sup>, -NHC(=O)R<sup>1b</sup>,  
15 -SO<sub>2</sub>NHR<sup>1b</sup>, -OR<sup>1b</sup>, -SR<sup>1b</sup>, C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl,  
C<sub>1</sub>-C<sub>6</sub> alkoxy, -S-(C<sub>1</sub>-C<sub>6</sub> alkyl),  
aryl substituted with 0-5 R<sup>1c</sup>,  
-O-(CH<sub>2</sub>)<sub>q</sub>-aryl substituted with 0-5 R<sup>1c</sup>,  
-S-(CH<sub>2</sub>)<sub>q</sub>-aryl substituted with 0-5 R<sup>1c</sup>, and  
20 5-10 membered heterocyclic group consisting of carbon  
atoms and 1-4 heteroatoms selected from the group:  
O, S, and N, and substituted with 0-3 R<sup>1c</sup>;

R<sup>1b</sup> is H,  
25 C<sub>1</sub>-C<sub>4</sub> alkyl substituted with 0-3 R<sup>1c</sup>,  
C<sub>2</sub>-C<sub>4</sub> alkenyl substituted with 0-3 R<sup>1c</sup>,  
C<sub>2</sub>-C<sub>4</sub> alkynyl substituted with 0-3 R<sup>1c</sup>,  
C<sub>3</sub>-C<sub>6</sub> cycloalkyl substituted with 0-5 R<sup>1c</sup>,  
C<sub>3</sub>-C<sub>6</sub> carbocycle substituted with 0-5 R<sup>1c</sup>,  
30 aryl substituted with 0-5 R<sup>1c</sup>, or  
5-6 membered heterocyclic group consisting of carbon  
atoms and 1-4 heteroatoms selected from the group:  
O, S, and N, said heterocyclic group substituted  
with 0-4 R<sup>1c</sup>;

35 R<sup>1c</sup> is selected at each occurrence from: C<sub>1</sub>-C<sub>4</sub> alkyl, Cl,  
F, Br, I, OH, C<sub>1</sub>-C<sub>4</sub> alkoxy, -CN, -NO<sub>2</sub>, C(O)OR<sup>1d</sup>,  
NR<sup>1d</sup>R<sup>1d</sup>, CF<sub>3</sub>, and OCF<sub>3</sub>;

5

R<sup>1d</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sup>2</sup> is H, F, or C<sub>1</sub>-C<sub>4</sub> alkyl;

10 R<sup>3</sup> is selected from the group: H,

C<sub>1</sub>-C<sub>6</sub> alkyl substituted with 0-4 R<sup>3a</sup>,

C<sub>2</sub>-C<sub>6</sub> alkenyl substituted with 0-4 R<sup>3a</sup>,

C<sub>2</sub>-C<sub>6</sub> alkynyl substituted with 0-4 R<sup>3a</sup>,

-(CH<sub>2</sub>)<sub>q</sub>- C<sub>3</sub>-C<sub>6</sub> cycloalkyl substituted with 0-4 R<sup>3b</sup>,

15 -(CH<sub>2</sub>)<sub>q</sub>-aryl substituted with 0-5 R<sup>3b</sup>, or

-(CH<sub>2</sub>)<sub>q</sub>-5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, and said heterocyclic group is substituted with 0-2 R<sup>3b</sup>;

20

R<sup>3a</sup> is selected from the group: -CO<sub>2</sub>R<sup>11</sup>, -NR<sup>11</sup>R<sup>11</sup>, -OR<sup>11</sup>, -SR<sup>11</sup>, -C(=NH)NH<sub>2</sub>, and aryl substituted with R<sup>10b</sup>;

R<sup>3b</sup> is selected from the group: -CO<sub>2</sub>H, -NH<sub>2</sub>, -OH, -SH, and  
25 -C(=NH)NH<sub>2</sub>;

R<sup>3c</sup> is, at each occurrence, independently selected from: H, C<sub>1</sub>-C<sub>6</sub> alkyl, -OH, and OR<sup>3d</sup>;

30 R<sup>3d</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl,

-(CH<sub>2</sub>)<sub>q</sub>- C<sub>3</sub>-C<sub>6</sub> cycloalkyl, -(CH<sub>2</sub>)<sub>q</sub>-aryl, or

-(CH<sub>2</sub>)<sub>q</sub>-(5-10 membered heterocyclic group), wherein said heterocyclic group consists of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N;

35

R<sup>4</sup> is selected from the group: H, C<sub>1</sub>-C<sub>6</sub> alkyl, phenyl, phenylmethyl-, phenylethyl-, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkylmethyl-, and C<sub>3</sub>-C<sub>6</sub> cycloalkylethyl-;

5

R<sup>5</sup> and R<sup>7</sup> are independently H or R<sup>3</sup>;

R<sup>6</sup> and R<sup>8</sup> are independently H or R<sup>4</sup>;

- 10 R<sup>9</sup> is selected from the group: -S(=O)R<sup>9a</sup>, -S(=O)<sub>2</sub>R<sup>9a</sup>,  
-C(=O)R<sup>9a</sup>, -C(=O)OR<sup>9a</sup>, -C(=O)NHR<sup>9a</sup>, C<sub>1</sub>-C<sub>3</sub> alkyl-R<sup>9a</sup>,  
C<sub>2</sub>-C<sub>6</sub> alkenyl-R<sup>9a</sup>, and C<sub>2</sub>-C<sub>6</sub> alkynyl-R<sup>9a</sup>;

R<sup>9a</sup> is selected from the group:

- 15 C<sub>1</sub>-C<sub>6</sub> alkyl substituted with 0-3 R<sup>9b</sup>,  
C<sub>3</sub>-C<sub>6</sub> cycloalkyl substituted with 0-3 R<sup>9c</sup>,  
aryl substituted with 0-3 R<sup>9c</sup>, and  
5-14 membered heterocyclic group consisting of carbon  
atoms and 1-4 heteroatoms selected from the  
20 group: O, S, and N, and said heterocyclic group  
is substituted with 0-3 R<sup>9c</sup>;

R<sup>9b</sup> is selected from the group: phenyl, naphthyl, benzyl,  
and 5-10 membered heterocyclic group consisting of  
25 carbon atoms and 1-4 heteroatoms selected from the  
group: O, S, and N, and R<sup>9b</sup> is substituted with 0-3  
R<sup>9c</sup>;

R<sup>9c</sup> is selected at each occurrence from the group:

- 30 CF<sub>3</sub>, OCF<sub>3</sub>, Cl, F, Br, I, =O, OH, phenyl, C(O)OR<sup>11</sup>, NH<sub>2</sub>,  
NH(CH<sub>3</sub>), N(CH<sub>3</sub>)<sub>2</sub>, -CN, NO<sub>2</sub>;  
C<sub>1</sub>-C<sub>4</sub> alkyl substituted with 0-3 R<sup>9d</sup>,  
C<sub>1</sub>-C<sub>4</sub> alkoxy substituted with 0-3 R<sup>9d</sup>,  
C<sub>3</sub>-C<sub>6</sub> cycloalkyl substituted with 0-3 R<sup>9d</sup>,  
35 aryl substituted with 0-5 R<sup>9d</sup>, and  
5-6 membered heterocyclic group consisting of carbon  
atoms and 1-4 heteroatoms selected from the  
group: O, S, and N, and said heterocyclic group  
is substituted with 0-4 R<sup>9d</sup>;

5

R<sup>9d</sup> is selected at each occurrence from the group:

C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CF<sub>3</sub>, OCF<sub>3</sub>, Cl, F, Br, I, =O, OH, phenyl, C(O)OR<sup>11</sup>, NH<sub>2</sub>, NH(CH<sub>3</sub>), N(CH<sub>3</sub>)<sub>2</sub>, -CN, and NO<sub>2</sub>;

10

an amino acid residue, at each occurrence, independently comprises a natural amino acid, a modified amino acid or an unnatural amino acid wherein said natural, modified or unnatural amino acid is of either D or L configuration;

15

n is 1, 2, 3, or 4; and

p is 1 or 2; and

20

q, at each occurrence, is independently 0, 1 or 2.

[2] In a preferred embodiment, the present invention provides novel compounds of Formula I, wherein:

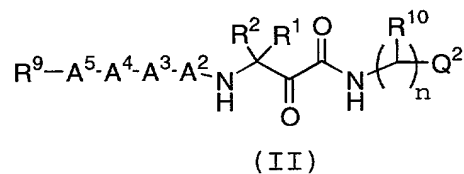
25

Q is -(CR<sup>10</sup>R<sup>10c</sup>)<sub>n</sub>-Q<sup>2</sup> or

an amino acid residue, wherein the amino acid residue comprises a natural, a modified or an unnatural amino acid.

30

[3] In a more preferred embodiment, the present invention provides novel compounds of Formula II, wherein:



35

or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

- 5  $R^{10}$  is selected from the group:  $-\text{CO}_2R^{11}$ ,  $-\text{NR}^{11}R^{11}$ , and  $\text{C}_1\text{-C}_6$  alkyl substituted with 0-1  $R^{10a}$ ;
- $R^{10a}$  is selected from the group: halo,  $-\text{NO}_2$ ,  $-\text{CN}$ ,  $-\text{CF}_3$ ,  
10  $-\text{CO}_2R^{11}$ ,  $-\text{NR}^{11}R^{11}$ ,  $-\text{OR}^{11}$ ,  $-\text{SR}^{11}$ ,  $-\text{C}(=\text{NH})\text{NH}_2$ , and aryl substituted with 0-1  $R^{10b}$ ;
- $R^{10b}$  is selected from the group:  $-\text{CO}_2\text{H}$ ,  $-\text{NH}_2$ ,  $-\text{OH}$ ,  $-\text{SH}$ , and  
 $-\text{C}(=\text{NH})\text{NH}_2$ ;
- 15  $R^{10c}$  is H or  $\text{C}_1\text{-C}_4$  alkyl;
- alternatively,  $R^{10}$  and  $R^{10c}$  can be combined to form a  $\text{C}_3\text{-C}_6$  cycloalkyl group substituted with 0-1  $R^{10a}$ ;
- 20  $R^{11}$  is, at each occurrence, independently H or  $\text{C}_1\text{-C}_4$  alkyl;
- $R^{11a}$  is H,  $\text{C}_1\text{-C}_4$  alkyl,  $\text{C}_1\text{-C}_4$  haloalkyl,  $\text{C}_2\text{-C}_4$  alkenyl,  
 $\text{C}_2\text{-C}_4$  alkynyl, aryl, aryl( $\text{C}_1\text{-C}_4$  alkyl)-,  
 $\text{C}_3\text{-C}_6$  cycloalkyl, or  $\text{C}_3\text{-C}_6$  cycloalkyl( $\text{C}_1\text{-C}_4$  alkyl)-;
- 25  $Q^2$  is  $-\text{X-NR}^{12}\text{-Z}$ ,  $-\text{NR}^{12}\text{-Y-Z}$ , or  $-\text{X-NR}^{12}\text{-Y-Z}$ ;
- $\text{X}$  is selected from the group:  $-\text{C}(=\text{O})-$ ,  $-\text{S}-$ ,  $-\text{S}(=\text{O})-$ ,  
 $-\text{S}(=\text{O})_2-$ ,  $-\text{P}(\text{O})-$ ,  $-\text{P}(\text{O})_2-$ , and  $-\text{P}(\text{O})_3-$ ;
- 30  $\text{Y}$  is selected from the group:  $-\text{C}(=\text{O})-$ ,  $-\text{S}-$ ,  $-\text{S}(=\text{O})-$ ,  
 $-\text{S}(=\text{O})_2-$ ,  $-\text{P}(\text{O})-$ ,  $-\text{P}(\text{O})_2-$ , and  $-\text{P}(\text{O})_3-$ ;
- $R^{12}$  is H or  $\text{C}_1\text{-C}_4$  alkyl;
- 35  $\text{Z}$  is  $\text{C}_1\text{-C}_4$  haloalkyl,  
 $\text{C}_1\text{-C}_4$  alkyl substituted with 0-3  $\text{Z}^a$ ,  
 $\text{C}_2\text{-C}_4$  alkenyl substituted with 0-3  $\text{Z}^a$ ,  
 $\text{C}_2\text{-C}_4$  alkynyl substituted with 0-3  $\text{Z}^a$ ,

- 5 C<sub>3</sub>-C<sub>10</sub> cycloalkyl substituted with 0-5 Z<sup>b</sup>,  
C<sub>3</sub>-C<sub>10</sub> carbocycle substituted with 0-5 Z<sup>b</sup>,  
aryl substituted with 0-5 Z<sup>b</sup>,  
5-10 membered heterocyclic group consisting of carbon  
atoms and 1-4 heteroatoms selected from the group:  
10 O, S, and N, said heterocyclic group substituted  
with 0-4 Z<sup>b</sup>;  
an amino acid residue, or  
-A<sup>7</sup>-A<sup>8</sup>-A<sup>9</sup>;
- 15 Z<sup>a</sup> is H, F, Cl, Br, I, -NO<sub>2</sub>, -CN, -NCS, -CF<sub>3</sub>, -OCF<sub>3</sub>,  
-CH<sub>3</sub>, -OCH<sub>3</sub>, -CO<sub>2</sub>R<sup>20</sup>, -C(=O)NR<sup>20</sup>R<sup>20</sup>, -NHC(=O)R<sup>20</sup>,  
-NR<sup>20</sup>R<sup>20</sup>, -OR<sup>20</sup>, -SR<sup>20</sup>, -S(=O)R<sup>20</sup>, -SO<sub>2</sub>R<sup>20</sup>, -SO<sub>2</sub>NR<sup>20</sup>R<sup>20</sup>,  
C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkyl,  
C<sub>1</sub>-C<sub>4</sub> haloalkoxy,
- 20 C<sub>3</sub>-C<sub>10</sub> cycloalkyl substituted with 0-5 Z<sup>b</sup>,  
C<sub>3</sub>-C<sub>10</sub> carbocycle substituted with 0-5 Z<sup>b</sup>,  
aryl substituted with 0-5 Z<sup>b</sup>, or  
5-10 membered heterocyclic group consisting of carbon  
atoms and 1-4 heteroatoms selected from the group:  
25 O, S, and N, said heterocyclic group substituted  
with 0-4 Z<sup>b</sup>;
- Z<sup>b</sup> is H, F, Cl, Br, I, -NO<sub>2</sub>, -CN, -NCS, -CF<sub>3</sub>, -OCF<sub>3</sub>,  
30 -CH<sub>3</sub>, -OCH<sub>3</sub>, -CO<sub>2</sub>R<sup>20</sup>, -C(=O)NR<sup>20</sup>R<sup>20</sup>, -NHC(=O)R<sup>20</sup>,  
-NR<sup>20</sup>R<sup>20</sup>, -OR<sup>20</sup>, -SR<sup>20</sup>, -S(=O)R<sup>20</sup>, -SO<sub>2</sub>R<sup>20</sup>, -SO<sub>2</sub>NR<sup>20</sup>R<sup>20</sup>,  
C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkyl,  
C<sub>1</sub>-C<sub>4</sub> haloalkoxy,
- 35 C<sub>3</sub>-C<sub>10</sub> cycloalkyl substituted with 0-5 Z<sup>c</sup>,  
C<sub>3</sub>-C<sub>10</sub> carbocycle substituted with 0-5 Z<sup>c</sup>,  
aryl substituted with 0-5 Z<sup>c</sup>, or  
5-10 membered heterocyclic group consisting of carbon  
atoms and 1-4 heteroatoms selected from the group:

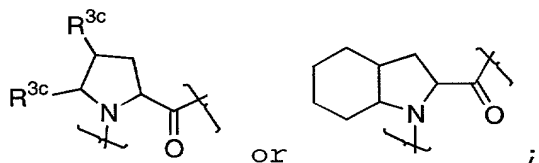
5 O, S, and N, said heterocyclic group substituted  
with 0-4 Z<sup>c</sup>;

Z<sup>c</sup> is H, F, Cl, Br, I, -NO<sub>2</sub>, -CN, -NCS, -CF<sub>3</sub>, -OCF<sub>3</sub>,  
-CH<sub>3</sub>, -OCH<sub>3</sub>, -CO<sub>2</sub>R<sup>20</sup>, -C(=O)NR<sup>20</sup>R<sup>20</sup>, -NHC(=O)R<sup>20</sup>,  
10 -NR<sup>20</sup>R<sup>20</sup>, -OR<sup>20</sup>, -SR<sup>20</sup>, -S(=O)R<sup>20</sup>, -SO<sub>2</sub>R<sup>20</sup>, -SO<sub>2</sub>NR<sup>20</sup>R<sup>20</sup>,  
C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkyl, or C<sub>1</sub>-C<sub>4</sub>  
haloalkoxy;

R<sup>20</sup> is H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, aryl,  
15 aryl(C<sub>1</sub>-C<sub>4</sub> alkyl)-, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or  
C<sub>3</sub>-C<sub>6</sub> cycloalkyl(C<sub>1</sub>-C<sub>4</sub> alkyl)-;

alternatively, NR<sup>20</sup>R<sup>20</sup> may form a 5-6 membered heterocyclic  
group consisting of carbon atoms, a nitrogen atom, and  
20 optionally a second heteroatom selected from the  
group: O, S, and N;

A<sup>2</sup> is a bond, -NH-CR<sup>3</sup>R<sup>4</sup>-C(=O)-, an amino acid residue,



25 A<sup>3</sup> is a bond, -NH-CR<sup>5</sup>R<sup>6</sup>-C(=O)-, or an amino acid residue;

A<sup>4</sup> is a bond, -NH-CR<sup>7</sup>R<sup>8</sup>-C(=O)-, or an amino acid residue;

30 A<sup>5</sup> is a bond or an amino acid residue;

A<sup>7</sup> is a bond or an amino acid residue;

A<sup>8</sup> is an amino acid residue;

35 A<sup>9</sup> is an amino acid residue;



5  $R^{1a}$  is selected from the group: H, F,  
      $C_1-C_6$  alkyl substituted with 0-3  $R^{1a}$ ,  
      $C_2-C_6$  alkenyl substituted with 0-3  $R^{1a}$ ,  
      $C_2-C_6$  alkynyl substituted with 0-3  $R^{1a}$ , and  
      $C_3-C_6$  cycloalkyl substituted with 0-3  $R^{1a}$ ;  
 10  
 $R^{1a}$  is selected at each occurrence from the group:  
     Cl, F, Br, I,  $CF_3$ ,  $CHF_2$ , OH, =O, SH,  $-CO_2R^{1b}$ ,  $-SO_2R^{1b}$ ,  
      $-SO_3R^{1b}$ ,  $-P(O)_2R^{1b}$ ,  $-P(O)_3R^{1b}$ ,  $-C(=O)NHR^{1b}$ ,  $-NHC(=O)R^{1b}$ ,  
      $-SO_2NHR^{1b}$ ,  $-OR^{1b}$ ,  $-SR^{1b}$ ,  $C_1-C_3$  alkyl,  $C_3-C_6$  cycloalkyl,  
 15  $C_1-C_6$  alkoxy,  $-S-(C_1-C_6 \text{ alkyl})$ ,  
     aryl substituted with 0-5  $R^{1c}$ ,  
      $-O-(CH_2)_q$ -aryl substituted with 0-5  $R^{1c}$ ,  
      $-S-(CH_2)_q$ -aryl substituted with 0-5  $R^{1c}$ , and  
     5-10 membered heterocyclic group consisting of carbon  
 20 atoms and 1-4 heteroatoms selected from the group:  
     O, S, and N, and substituted with 0-3  $R^{1c}$ ;  
  
 $R^{1b}$  is H,  
      $C_1-C_4$  alkyl substituted with 0-3  $R^{1c}$ ,  
 25  $C_2-C_4$  alkenyl substituted with 0-3  $R^{1c}$ ,  
      $C_2-C_4$  alkynyl substituted with 0-3  $R^{1c}$ ,  
      $C_3-C_6$  cycloalkyl substituted with 0-5  $R^{1c}$ ,  
      $C_3-C_6$  carbocycle substituted with 0-5  $R^{1c}$ ,  
     aryl substituted with 0-5  $R^{1c}$ , or  
 30 5-6 membered heterocyclic group consisting of carbon  
     atoms and 1-4 heteroatoms selected from the group:  
     O, S, and N, said heterocyclic group substituted  
     with 0-4  $R^{1c}$ ;  
  
 35  $R^{1c}$  is selected at each occurrence from:  $C_1-C_4$  alkyl, Cl,  
     F, Br, I, OH,  $C_1-C_4$  alkoxy,  $-CN$ ,  $-NO_2$ ,  $C(O)OR^{1d}$ ,  
      $NR^{1d}R^{1d}$ ,  $CF_3$ , and  $OCF_3$ ;

5  $R^{1d}$  is H or  $C_1$ - $C_4$  alkyl;

$R^2$  is H, F, or  $C_1$ - $C_4$  alkyl;

$R^3$  is selected from the group: H,

- 10  $C_1$ - $C_6$  alkyl substituted with 0-4  $R^{3a}$ ,  
 $C_2$ - $C_6$  alkenyl substituted with 0-4  $R^{3a}$ ,  
 $C_2$ - $C_6$  alkynyl substituted with 0-4  $R^{3a}$ ,  
-( $CH_2$ )<sub>q</sub>-  $C_3$ - $C_6$  cycloalkyl substituted with 0-4  $R^{3b}$ ,  
-( $CH_2$ )<sub>q</sub>-aryl substituted with 0-5  $R^{3b}$ , and  
15 -( $CH_2$ )<sub>q</sub>-5-10 membered heterocyclic group consisting of  
carbon atoms and 1-4 heteroatoms selected from  
the group: O, S, and N, and said heterocyclic  
group is substituted with 0-2  $R^{3b}$ ;

- 20  $R^{3a}$  is selected from the group:  $-CO_2R^{11}$ ,  $-NR^{11}R^{11}$ ,  $-OR^{11}$ ,  
 $-SR^{11}$ ,  $-C(=NH)NH_2$ , and aryl substituted with  $R^{10b}$ ;

$R^{3b}$  is selected from the group:  $-CO_2H$ ,  $-NH_2$ ,  $-OH$ ,  $-SH$ , and  
 $-C(=NH)NH_2$ ;

- 25  $R^{3c}$  is, at each occurrence, independently selected from: H,  
 $C_1$ - $C_6$  alkyl,  $-OH$ , and  $OR^{3d}$ ;

- $R^{3d}$  is  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl,  
30 -( $CH_2$ )<sub>q</sub>-  $C_3$ - $C_6$  cycloalkyl, -( $CH_2$ )<sub>q</sub>-aryl, or  
-( $CH_2$ )<sub>q</sub>-(5-10 membered heterocyclic group), wherein  
said heterocyclic group consists of carbon atoms  
and 1-4 heteroatoms selected from the group: O,  
S, and N;

- 35  $R^4$  is selected from the group: H,  $C_1$ - $C_6$  alkyl, phenyl,  
phenylmethyl-, phenylethyl-,  $C_3$ - $C_6$  cycloalkyl,  
 $C_3$ - $C_6$  cycloalkylmethyl-, and  $C_3$ - $C_6$  cycloalkylethyl-;

5 R<sup>5</sup> and R<sup>7</sup> are independently H or R<sup>3</sup>;

R<sup>6</sup> and R<sup>8</sup> are independently H or R<sup>4</sup>;

R<sup>9</sup> is selected from the group: -S(=O)R<sup>9a</sup>, -S(=O)<sub>2</sub>R<sup>9a</sup>,  
10 -C(=O)R<sup>9a</sup>, -C(=O)OR<sup>9a</sup>, -C(=O)NHR<sup>9a</sup>, C<sub>1</sub>-C<sub>3</sub> alkyl-R<sup>9a</sup>,  
C<sub>2</sub>-C<sub>6</sub> alkenyl-R<sup>9a</sup>, and C<sub>2</sub>-C<sub>6</sub> alkynyl-R<sup>9a</sup>;

R<sup>9a</sup> is selected from the group:

C<sub>1</sub>-C<sub>6</sub> alkyl substituted with 0-3 R<sup>9b</sup>,  
15 C<sub>3</sub>-C<sub>6</sub> cycloalkyl substituted with 0-3 R<sup>9c</sup>,  
aryl substituted with 0-3 R<sup>9c</sup>, and  
5-14 membered heterocyclic group consisting of carbon  
atoms and 1-4 heteroatoms selected from the  
group: O, S, and N, and said heterocyclic group  
20 is substituted with 0-3 R<sup>9c</sup>;

R<sup>9b</sup> is selected from the group: phenyl, naphthyl, benzyl,  
and 5-10 membered heterocyclic group consisting of  
carbon atoms and 1-4 heteroatoms selected from the  
25 group: O, S, and N, and R<sup>9b</sup> is substituted with 0-3  
R<sup>9c</sup>;

R<sup>9c</sup> is selected at each occurrence from the group:

CF<sub>3</sub>, OCF<sub>3</sub>, Cl, F, Br, I, =O, OH, phenyl, C(O)OR<sup>11</sup>, NH<sub>2</sub>,  
30 NH(CH<sub>3</sub>), N(CH<sub>3</sub>)<sub>2</sub>, -CN, NO<sub>2</sub>;  
C<sub>1</sub>-C<sub>4</sub> alkyl substituted with 0-3 R<sup>9d</sup>,  
C<sub>1</sub>-C<sub>4</sub> alkoxy substituted with 0-3 R<sup>9d</sup>,  
C<sub>3</sub>-C<sub>6</sub> cycloalkyl substituted with 0-3 R<sup>9d</sup>,  
aryl substituted with 0-5 R<sup>9d</sup>, and  
35 5-6 membered heterocyclic group consisting of carbon  
atoms and 1-4 heteroatoms selected from the  
group: O, S, and N, and said heterocyclic group  
is substituted with 0-4 R<sup>9d</sup>;

5 R<sup>9d</sup> is selected at each occurrence from the group:  
C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CF<sub>3</sub>, OCF<sub>3</sub>, Cl, F, Br, I, =O,  
OH, phenyl, C(O)OR<sup>11</sup>, NH<sub>2</sub>, NH(CH<sub>3</sub>), N(CH<sub>3</sub>)<sub>2</sub>, -CN, and  
NO<sub>2</sub>;

10 n is 1, 2, or 3; and

p is 1 or 2; and

q, at each occurrence, is independently 0, 1 or 2.

15 [4] In a further more preferred embodiment, the present  
invention provides novel compounds of Formula II, wherein:

R<sup>10</sup> is selected from the group: -CO<sub>2</sub>R<sup>11</sup>, -NR<sup>11</sup>R<sup>11</sup>, and C<sub>1</sub>-C<sub>6</sub>  
20 alkyl substituted with 0-1 R<sup>10a</sup>;

R<sup>10a</sup> is selected from the group: halo, -NO<sub>2</sub>, -CN, -CF<sub>3</sub>,  
-CO<sub>2</sub>R<sup>11</sup>, -NR<sup>11</sup>R<sup>11</sup>, -OR<sup>11</sup>, -SR<sup>11</sup>, -C(=NH)NH<sub>2</sub>, and aryl  
substituted with 0-1 R<sup>10b</sup>;

25 R<sup>10b</sup> is selected from the group: -CO<sub>2</sub>H, -NH<sub>2</sub>, -OH, -SH, and  
-C(=NH)NH<sub>2</sub>;

R<sup>10c</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

30 alternatively, R<sup>10</sup> and R<sup>10c</sup> can be combined to form a C<sub>3</sub>-C<sub>6</sub>  
cycloalkyl group substituted with 0-1 R<sup>10a</sup>;

R<sup>11</sup> is, at each occurrence, independently H or C<sub>1</sub>-C<sub>4</sub> alkyl;

35 R<sup>11a</sup> is H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl,  
C<sub>2</sub>-C<sub>4</sub> alkynyl, aryl, aryl(C<sub>1</sub>-C<sub>4</sub> alkyl)-,  
C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or C<sub>3</sub>-C<sub>6</sub> cycloalkyl(C<sub>1</sub>-C<sub>4</sub> alkyl)-;

5 Q<sup>2</sup> is -X-NR<sup>12</sup>-Z, -NR<sup>12</sup>-Y-Z, or -X-NR<sup>12</sup>-Y-Z;

X is selected from the group: -C(=O)-, -S-, -S(=O)-, and  
-S(=O)<sub>2</sub>-;

10 Y is selected from the group: -C(=O)-, -S-, -S(=O)-, and  
-S(=O)<sub>2</sub>-;

R<sup>12</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

15 Z is C<sub>1</sub>-C<sub>4</sub> haloalkyl,  
C<sub>1</sub>-C<sub>4</sub> alkyl substituted with 0-3 Z<sup>a</sup>,  
C<sub>2</sub>-C<sub>4</sub> alkenyl substituted with 0-3 Z<sup>a</sup>,  
C<sub>2</sub>-C<sub>4</sub> alkynyl substituted with 0-3 Z<sup>a</sup>,  
C<sub>3</sub>-C<sub>10</sub> cycloalkyl substituted with 0-5 Z<sup>b</sup>,  
20 C<sub>3</sub>-C<sub>10</sub> carbocycle substituted with 0-5 Z<sup>b</sup>,  
aryl substituted with 0-5 Z<sup>b</sup>,  
5-10 membered heterocyclic group consisting of carbon  
atoms and 1-4 heteroatoms selected from the group:  
O, S, and N, said heterocyclic group substituted  
25 with 0-4 Z<sup>b</sup>;  
an amino acid residue, or  
-A<sup>7</sup>-A<sup>8</sup>-A<sup>9</sup>;

Z<sup>a</sup> is H, F, Cl, Br, I, -NO<sub>2</sub>, -CN, -NCS, -CF<sub>3</sub>, -OCF<sub>3</sub>,  
30 -CH<sub>3</sub>, -OCH<sub>3</sub>, -CO<sub>2</sub>R<sup>20</sup>, -C(=O)NR<sup>20</sup>R<sup>20</sup>, -NHC(=O)R<sup>20</sup>,  
-NR<sup>20</sup>R<sup>20</sup>, -OR<sup>20</sup>, -SR<sup>20</sup>, -S(=O)R<sup>20</sup>, -SO<sub>2</sub>R<sup>20</sup>, -SO<sub>2</sub>NR<sup>20</sup>R<sup>20</sup>,  
C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkyl,  
C<sub>1</sub>-C<sub>4</sub> haloalkoxy,

35 C<sub>3</sub>-C<sub>10</sub> cycloalkyl substituted with 0-5 Z<sup>b</sup>,  
C<sub>3</sub>-C<sub>10</sub> carbocycle substituted with 0-5 Z<sup>b</sup>,  
aryl substituted with 0-5 Z<sup>b</sup>, or  
5-10 membered heterocyclic group consisting of carbon  
atoms and 1-4 heteroatoms selected from the group:

5 O, S, and N, said heterocyclic group substituted  
with 0-4 Z<sup>b</sup>;

Z<sup>b</sup> is H, F, Cl, Br, I, -NO<sub>2</sub>, -CN, -NCS, -CF<sub>3</sub>, -OCF<sub>3</sub>,  
-CH<sub>3</sub>, -OCH<sub>3</sub>, -CO<sub>2</sub>R<sup>20</sup>, -C(=O)NR<sup>20</sup>R<sup>20</sup>, -NHC(=O)R<sup>20</sup>,  
10 -NR<sup>20</sup>R<sup>20</sup>, -OR<sup>20</sup>, -SR<sup>20</sup>, -S(=O)R<sup>20</sup>, -SO<sub>2</sub>R<sup>20</sup>, -SO<sub>2</sub>NR<sup>20</sup>R<sup>20</sup>,  
C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkyl,  
C<sub>1</sub>-C<sub>4</sub> haloalkoxy,

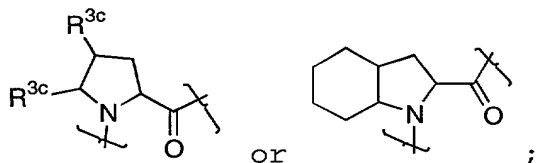
C<sub>3</sub>-C<sub>10</sub> cycloalkyl substituted with 0-5 Z<sup>c</sup>,  
15 C<sub>3</sub>-C<sub>10</sub> carbocycle substituted with 0-5 Z<sup>c</sup>,  
aryl substituted with 0-5 Z<sup>c</sup>, or  
5-10 membered heterocyclic group consisting of carbon  
atoms and 1-4 heteroatoms selected from the group:  
O, S, and N, said heterocyclic group substituted  
20 with 0-4 Z<sup>c</sup>;

Z<sup>c</sup> is H, F, Cl, Br, I, -NO<sub>2</sub>, -CN, -NCS, -CF<sub>3</sub>, -OCF<sub>3</sub>,  
-CH<sub>3</sub>, -OCH<sub>3</sub>, -CO<sub>2</sub>R<sup>20</sup>, -C(=O)NR<sup>20</sup>R<sup>20</sup>, -NHC(=O)R<sup>20</sup>,  
-NR<sup>20</sup>R<sup>20</sup>, -OR<sup>20</sup>, -SR<sup>20</sup>, -S(=O)R<sup>20</sup>, -SO<sub>2</sub>R<sup>20</sup>, -SO<sub>2</sub>NR<sup>20</sup>R<sup>20</sup>,  
25 C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkyl, or C<sub>1</sub>-C<sub>4</sub>  
haloalkoxy;

R<sup>20</sup> is H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, aryl,  
aryl(C<sub>1</sub>-C<sub>4</sub> alkyl)-, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or  
30 C<sub>3</sub>-C<sub>6</sub> cycloalkyl(C<sub>1</sub>-C<sub>4</sub> alkyl)-;

alternatively, NR<sup>20</sup>R<sup>20</sup> may form a piperidinyl, piperazinyl,  
or morpholinyl group;

35 A<sup>2</sup> is a bond, -NH-CR<sup>3</sup>R<sup>4</sup>-C(=O)-, an amino acid residue,



5

A<sup>3</sup> is a bond or an amino acid residue;

A<sup>4</sup> is a bond or an amino acid residue;

10 A<sup>5</sup> is a bond;

R<sup>1</sup> is selected from the group: H,

C<sub>1</sub>-C<sub>6</sub> alkyl substituted with 0-3 R<sup>1a</sup>,

C<sub>2</sub>-C<sub>6</sub> alkenyl substituted with 0-3 R<sup>1a</sup>,

15 C<sub>2</sub>-C<sub>6</sub> alkynyl substituted with 0-3 R<sup>1a</sup>, and

C<sub>3</sub>-C<sub>6</sub> cycloalkyl substituted with 0-3 R<sup>1a</sup>;

R<sup>1a</sup> is selected at each occurrence from the group:

Cl, F, Br, I, CF<sub>3</sub>, CHF<sub>2</sub>, OH, =O, SH, -CO<sub>2</sub>R<sup>1b</sup>, -SO<sub>2</sub>R<sup>1b</sup>,

20 -SO<sub>3</sub>R<sup>1b</sup>, -P(O)<sub>2</sub>R<sup>1b</sup>, -P(O)<sub>3</sub>R<sup>1b</sup>, -C(=O)NHR<sup>1b</sup>, -NHC(=O)R<sup>1b</sup>,

-SO<sub>2</sub>NHR<sup>1b</sup>, -OR<sup>1b</sup>, -SR<sup>1b</sup>, C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl,

C<sub>1</sub>-C<sub>6</sub> alkoxy, -S-(C<sub>1</sub>-C<sub>6</sub> alkyl),

aryl substituted with 0-5 R<sup>1c</sup>,

-O-(CH<sub>2</sub>)<sub>q</sub>-aryl substituted with 0-5 R<sup>1c</sup>,

25 -S-(CH<sub>2</sub>)<sub>q</sub>-aryl substituted with 0-5 R<sup>1c</sup>, and

5-10 membered heterocyclic group consisting of carbon  
atoms and 1-4 heteroatoms selected from the group:

O, S, and N, and substituted with 0-3 R<sup>1c</sup>;

30 R<sup>1b</sup> is H,

C<sub>1</sub>-C<sub>4</sub> alkyl substituted with 0-3 R<sup>1c</sup>,

C<sub>2</sub>-C<sub>4</sub> alkenyl substituted with 0-3 R<sup>1c</sup>,

C<sub>2</sub>-C<sub>4</sub> alkynyl substituted with 0-3 R<sup>1c</sup>,

C<sub>3</sub>-C<sub>6</sub> cycloalkyl substituted with 0-5 R<sup>1c</sup>,

35 C<sub>3</sub>-C<sub>6</sub> carbocycle substituted with 0-5 R<sup>1c</sup>,

aryl substituted with 0-5 R<sup>1c</sup>, or

5-6 membered heterocyclic group consisting of carbon  
atoms and 1-4 heteroatoms selected from the group:

5 O, S, and N, said heterocyclic group substituted  
with 0-4 R<sup>1c</sup>;

R<sup>1c</sup> is selected at each occurrence from: C<sub>1</sub>-C<sub>4</sub> alkyl, Cl,  
F, Br, I, OH, C<sub>1</sub>-C<sub>4</sub> alkoxy, -CN, -NO<sub>2</sub>, C(O)OR<sup>1d</sup>,  
10 NR<sup>1d</sup>R<sup>1d</sup>, CF<sub>3</sub>, and OCF<sub>3</sub>;

R<sup>1d</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sup>2</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;  
15

R<sup>3</sup> is selected from the group: H,  
C<sub>1</sub>-C<sub>6</sub> alkyl substituted with 0-4 R<sup>3a</sup>,  
C<sub>2</sub>-C<sub>6</sub> alkenyl substituted with 0-4 R<sup>3a</sup>,  
C<sub>2</sub>-C<sub>6</sub> alkynyl substituted with 0-4 R<sup>3a</sup>,  
20 -(CH<sub>2</sub>)<sub>q</sub>- C<sub>3</sub>-C<sub>6</sub> cycloalkyl substituted with 0-4 R<sup>3b</sup>,  
-(CH<sub>2</sub>)<sub>q</sub>-aryl substituted with 0-5 R<sup>3b</sup>, and  
-(CH<sub>2</sub>)<sub>q</sub>-5-10 membered heterocyclic group consisting of  
carbon atoms and 1-4 heteroatoms selected from  
the group: O, S, and N, and said heterocyclic  
25 group is substituted with 0-2 R<sup>3b</sup>;

R<sup>3a</sup> is selected from the group: -CO<sub>2</sub>R<sup>11</sup>, -NR<sup>11</sup>R<sup>11</sup>, -OR<sup>11</sup>,  
-SR<sup>11</sup>, -C(=NH)NH<sub>2</sub>, and aryl substituted with R<sup>10b</sup>;

30 R<sup>3b</sup> is selected from the group: -CO<sub>2</sub>H, - NH<sub>2</sub>, -OH, -SH, and  
-C(=NH)NH<sub>2</sub>;

R<sup>3c</sup> is, at each occurrence, independently selected from: H,  
C<sub>1</sub>-C<sub>6</sub> alkyl, -OH, and OR<sup>3d</sup>;  
35

R<sup>3d</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl,  
-(CH<sub>2</sub>)<sub>q</sub>-C<sub>3</sub>-C<sub>6</sub> cycloalkyl, -(CH<sub>2</sub>)<sub>q</sub>-aryl, or  
-(CH<sub>2</sub>)<sub>q</sub>-(5-10 membered heterocyclic group), wherein  
said heterocyclic group consists of carbon atoms



5                   and 1-4 heteroatoms selected from the group: O,  
S, and N;

R<sup>4</sup> is selected from the group: H, C<sub>1</sub>-C<sub>6</sub> alkyl, phenyl,  
phenylmethyl-, phenylethyl-, C<sub>3</sub>-C<sub>6</sub> cycloalkyl,  
10       C<sub>3</sub>-C<sub>6</sub> cycloalkylmethyl-, and C<sub>3</sub>-C<sub>6</sub> cycloalkylethyl-;

R<sup>9</sup> is selected from the group: -S(=O)<sub>2</sub>R<sup>9a</sup>, -C(=O)R<sup>9a</sup>,  
C<sub>1</sub>-C<sub>3</sub> alkyl-R<sup>9a</sup>, C<sub>2</sub>-C<sub>6</sub> alkenyl-R<sup>9a</sup>, and  
C<sub>2</sub>-C<sub>6</sub> alkynyl-R<sup>9a</sup>;

15       R<sup>9a</sup> is selected from the group:  
C<sub>1</sub>-C<sub>6</sub> alkyl substituted with 0-3 R<sup>9b</sup>,  
C<sub>3</sub>-C<sub>6</sub> cycloalkyl substituted with 0-3 R<sup>9c</sup>,  
aryl substituted with 0-3 R<sup>9c</sup>, and  
20       5-14 membered heterocyclic group consisting of carbon  
atoms and 1-4 heteroatoms selected from the  
group: O, S, and N, and said heterocyclic group  
is substituted with 0-3 R<sup>9c</sup>;

25       R<sup>9b</sup> is selected from the group: phenyl, naphthyl, benzyl,  
and 5-10 membered heterocyclic group consisting of  
carbon atoms and 1-4 heteroatoms selected from the  
group: O, S, and N, and R<sup>9b</sup> is substituted with 0-3  
R<sup>9c</sup>;

30       R<sup>9c</sup> is selected at each occurrence from the group:  
CF<sub>3</sub>, OCF<sub>3</sub>, Cl, F, Br, I, =O, OH, phenyl, C(O)OR<sup>11</sup>, NH<sub>2</sub>,  
NH(CH<sub>3</sub>), N(CH<sub>3</sub>)<sub>2</sub>, -CN, NO<sub>2</sub>;  
C<sub>1</sub>-C<sub>4</sub> alkyl substituted with 0-3 R<sup>9d</sup>,  
35       C<sub>1</sub>-C<sub>4</sub> alkoxy substituted with 0-3 R<sup>9d</sup>,  
C<sub>3</sub>-C<sub>6</sub> cycloalkyl substituted with 0-3 R<sup>9d</sup>,  
aryl substituted with 0-5 R<sup>9d</sup>, and  
5-6 membered heterocyclic group consisting of carbon  
atoms and 1-4 heteroatoms selected from the

5 group: O, S, and N, and said heterocyclic group  
is substituted with 0-4 R<sup>9d</sup>;

R<sup>9d</sup> is selected at each occurrence from the group:

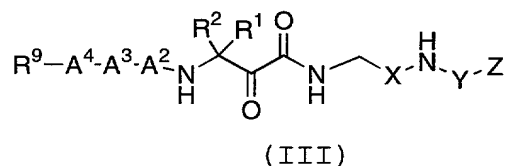
C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CF<sub>3</sub>, OCF<sub>3</sub>, Cl, F, Br, I, =O,  
10 OH, phenyl, C(O)OR<sup>11</sup>, NH<sub>2</sub>, NH(CH<sub>3</sub>), N(CH<sub>3</sub>)<sub>2</sub>, -CN, and  
NO<sub>2</sub>;

n is 1 or 2; and

15 p is 1 or 2; and

q, at each occurrence, is independently 0, 1 or 2.

[5] In an even more preferred embodiment, the present  
20 invention provides novel compounds of Formula III, wherein:



25 or a stereoisomer or pharmaceutically acceptable salt form  
thereof, wherein;

R<sup>11</sup> is, at each occurrence, independently H or C<sub>1</sub>-C<sub>4</sub> alkyl;

30 X is -C(=O)-, -S-, -S(=O)-, or -S(=O)<sub>2</sub>-;

Y is -C(=O)- or -S(=O)<sub>2</sub>-;

Z is C<sub>1</sub>-C<sub>4</sub> haloalkyl,

35 C<sub>1</sub>-C<sub>4</sub> alkyl substituted with 0-3 Z<sup>a</sup>,  
C<sub>2</sub>-C<sub>4</sub> alkenyl substituted with 0-3 Z<sup>a</sup>,  
C<sub>2</sub>-C<sub>4</sub> alkynyl substituted with 0-3 Z<sup>a</sup>,  
C<sub>3</sub>-C<sub>10</sub> cycloalkyl substituted with 0-5 Z<sup>b</sup>,

5 C<sub>3</sub>-C<sub>10</sub> carbocycle substituted with 0-5 Z<sup>b</sup>,  
 aryl substituted with 0-5 Z<sup>b</sup>, or  
 5-10 membered heterocyclic group consisting of carbon  
 atoms and 1-4 heteroatoms selected from the group:  
 pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl,  
 10 pyrazinyl, piperazinyl, piperidinyl, imidazolyl,  
 imidazolidinyl, indolyl, tetrazolyl, isoxazolyl,  
 morpholinyl, oxazolyl, oxazolidinyl,  
 tetrahydrofuranyl, thiadiazinyl, thiadiazolyl,  
 thiazolyl, triazinyl, triazolyl, benzimidazolyl,  
 15 1H-indazolyl, benzofuranyl, benzothiofuranyl,  
 benztetrazolyl, benzotriazolyl, benzisoxazolyl,  
 benzoxazolyl, oxindolyl, benzoxazolinyl,  
 benzthiazolyl, benzisothiazolyl, isatinoyl,  
 isoquinolinyl, octahydroisoquinolinyl,  
 20 tetrahydroisoquinolinyl, tetrahydroquinolinyl,  
 isoxazolopyridinyl, quinazolinyl, quinolinyl,  
 isothiazolopyridinyl, thiazolopyridinyl,  
 oxazolopyridinyl, imidazolopyridinyl, and  
 pyrazolopyridinyl; said heterocyclic group  
 25 substituted with 0-4 Z<sup>b</sup>;

Z<sup>a</sup> is H, F, Cl, Br, I, -NO<sub>2</sub>, -CN, -NCS, -CF<sub>3</sub>, -OCF<sub>3</sub>,  
 -CH<sub>3</sub>, -OCH<sub>3</sub>, -CO<sub>2</sub>R<sup>20</sup>, -C(=O)NR<sup>20</sup>R<sup>20</sup>, -NHC(=O)R<sup>20</sup>,  
 -NR<sup>20</sup>R<sup>20</sup>, -OR<sup>20</sup>, -SR<sup>20</sup>, -S(=O)R<sup>20</sup>, -SO<sub>2</sub>R<sup>20</sup>, -SO<sub>2</sub>NR<sup>20</sup>R<sup>20</sup>,  
 30 C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkyl,  
 C<sub>1</sub>-C<sub>4</sub> haloalkoxy,

C<sub>3</sub>-C<sub>10</sub> cycloalkyl substituted with 0-5 Z<sup>b</sup>,  
 C<sub>3</sub>-C<sub>10</sub> carbocycle substituted with 0-5 Z<sup>b</sup>,  
 35 aryl substituted with 0-5 Z<sup>b</sup>, or  
 5-10 membered heterocyclic group consisting of carbon  
 atoms and 1-4 heteroatoms selected from the group:  
 pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl,  
 pyrazinyl, piperazinyl, piperidinyl, imidazolyl,  
 40 imidazolidinyl, indolyl, tetrazolyl, isoxazolyl,

5 morpholinyl, oxazolyl, oxazolidinyl,  
 tetrahydrofuranyl, thiadiazinyl, thiadiazolyl,  
 thiazolyl, triazinyl, triazolyl, benzimidazolyl,  
 1*H*-indazolyl, benzofuranyl, benzothiofuranyl,  
 10 benztetrazolyl, benzotriazolyl, benzisoxazolyl,  
 benzoxazolyl, oxindolyl, benzoxazolinyl,  
 benzthiazolyl, benzisothiazolyl, isatinoyl,  
 isoquinolinyl, octahydroisoquinolinyl,  
 tetrahydroisoquinolinyl, tetrahydroquinolinyl,  
 isoxazolopyridinyl, quinazolinyl, quinolinyl,  
 15 isothiazolopyridinyl, thiazolopyridinyl,  
 oxazolopyridinyl, imidazolopyridinyl, and  
 pyrazolopyridinyl; said heterocyclic group  
 substituted with 0-4 Z<sup>b</sup>;

20 Z<sup>b</sup> is H, F, Cl, Br, I, -NO<sub>2</sub>, -CN, -NCS, -CF<sub>3</sub>, -OCF<sub>3</sub>,  
 -CH<sub>3</sub>, -OCH<sub>3</sub>, -CO<sub>2</sub>R<sup>20</sup>, -C(=O)NR<sup>20</sup>R<sup>20</sup>, -NHC(=O)R<sup>20</sup>,  
 -NR<sup>20</sup>R<sup>20</sup>, -OR<sup>20</sup>, -SR<sup>20</sup>, -S(=O)R<sup>20</sup>, -SO<sub>2</sub>R<sup>20</sup>, -SO<sub>2</sub>NR<sup>20</sup>R<sup>20</sup>,  
 C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkyl,  
 C<sub>1</sub>-C<sub>4</sub> haloalkoxy,

25 C<sub>3</sub>-C<sub>10</sub> cycloalkyl substituted with 0-5 Z<sup>c</sup>,  
 C<sub>3</sub>-C<sub>10</sub> carbocycle substituted with 0-5 Z<sup>c</sup>,  
 aryl substituted with 0-5 Z<sup>c</sup>, or  
 5-10 membered heterocyclic group consisting of carbon

30 atoms and 1-4 heteroatoms selected from the group:  
 pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl,  
 pyrazinyl, piperazinyl, piperidinyl, imidazolyl,  
 imidazolidinyl, indolyl, tetrazolyl, isoxazolyl,  
 morpholinyl, oxazolyl, oxazolidinyl,

35 tetrahydrofuranyl, thiadiazinyl, thiadiazolyl,  
 thiazolyl, triazinyl, triazolyl, benzimidazolyl,  
 1*H*-indazolyl, benzofuranyl, benzothiofuranyl,  
 benztetrazolyl, benzotriazolyl, benzisoxazolyl,  
 benzoxazolyl, oxindolyl, benzoxazolinyl,

40 benzthiazolyl, benzisothiazolyl, isatinoyl,  
 isoquinolinyl, octahydroisoquinolinyl,

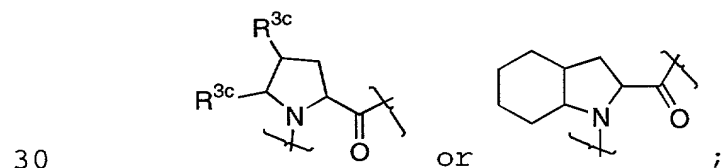
5 tetrahydroisoquinolinyl, tetrahydroquinolinyl,  
isoxazolopyridinyl, quinazolinyl, quinolinyl,  
isothiazolopyridinyl, thiazolopyridinyl,  
oxazolopyridinyl, imidazolopyridinyl, and  
pyrazolopyridinyl; said heterocyclic group  
10 substituted with 0-4  $Z^c$ ;

$Z^c$  is H, F, Cl, Br, I,  $-NO_2$ ,  $-CN$ ,  $-NCS$ ,  $-CF_3$ ,  $-OCF_3$ ,  
 $-CH_3$ ,  $-OCH_3$ ,  $-CO_2R^{20}$ ,  $-C(=O)NR^{20}R^{20}$ ,  $-NHC(=O)R^{20}$ ,  
 $-NR^{20}R^{20}$ ,  $-OR^{20}$ ,  $-SR^{20}$ ,  $-S(=O)R^{20}$ ,  $-SO_2R^{20}$ ,  $-SO_2NR^{20}R^{20}$ ,  
15  $C_1-C_4$  alkyl,  $C_1-C_4$  alkoxy,  $C_1-C_4$  haloalkyl, or  $C_1-C_4$   
haloalkoxy;

$R^{20}$  is H,  $C_1-C_4$  alkyl,  $C_1-C_4$  haloalkyl, aryl,  
aryl( $C_1-C_4$  alkyl)-,  $C_3-C_6$  cycloalkyl, or  
20  $C_3-C_6$  cycloalkyl( $C_1-C_4$  alkyl)-;

alternatively,  $NR^{20}R^{20}$  may form a piperidinyl, piperazinyl,  
or morpholinyl group;

25  $A^2$  is a bond,  $-NH-CR^3R^4-C(=O)-$ , Ala, Arg, Asn, Asp, Aze,  
Cha, Cys, Dpa, Gln, Glu, Gly, His, Hyp, Ile, Irg, Leu,  
Lys, Met, Orn, Phe, Phe(4-fluoro), Pro, Sar, Ser, Thr,  
Trp, Tyr, Val,



$A^3$  is a bond, Ala, Arg, Asn, Asp, Aze, Cha, Cys, Dpa, Gln,  
Glu, Gly, His, Hyp, Ile, Irg, Leu, Lys, Met, Orn, Phe,  
Phe(4-fluoro), Pro, Sar, Ser, Thr, Trp, Tyr, or Val;  
35

5 A<sup>4</sup> is a bond, Ala, Arg, Asn, Asp, Aze, Cha, Cys, Dpa, Gln, Glu, Gly, His, Hyp, Ile, Irg, Leu, Lys, Met, Orn, Phe, Phe(4-fluoro), Pro, Sar, Ser, Thr, Trp, Tyr, or Val;

R<sup>1</sup> is selected from the group: H,

10 C<sub>1</sub>-C<sub>6</sub> alkyl substituted with 0-3 R<sup>1a</sup>,  
C<sub>2</sub>-C<sub>6</sub> alkenyl substituted with 0-3 R<sup>1a</sup>,  
C<sub>2</sub>-C<sub>6</sub> alkynyl substituted with 0-3 R<sup>1a</sup>, and  
C<sub>3</sub>-C<sub>6</sub> cycloalkyl substituted with 0-3 R<sup>1a</sup>;

15 R<sup>1a</sup> is selected at each occurrence from the group:

Cl, F, Br, I, CF<sub>3</sub>, CHF<sub>2</sub>, OH, =O, SH, -CO<sub>2</sub>R<sup>1b</sup>, -SO<sub>2</sub>R<sup>1b</sup>,  
-SO<sub>3</sub>R<sup>1b</sup>, -P(O)<sub>2</sub>R<sup>1b</sup>, -P(O)<sub>3</sub>R<sup>1b</sup>, -C(=O)NHR<sup>1b</sup>, -NHC(=O)R<sup>1b</sup>,  
-SO<sub>2</sub>NHR<sup>1b</sup>, -OR<sup>1b</sup>, -SR<sup>1b</sup>, C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl,  
C<sub>1</sub>-C<sub>6</sub> alkoxy, -S-(C<sub>1</sub>-C<sub>6</sub> alkyl),

20 aryl substituted with 0-5 R<sup>1c</sup>,  
-O-(CH<sub>2</sub>)<sub>q</sub>-aryl substituted with 0-5 R<sup>1c</sup>,  
-S-(CH<sub>2</sub>)<sub>q</sub>-aryl substituted with 0-5 R<sup>1c</sup>, and  
5-10 membered heterocyclic group consisting of carbon

atoms and 1-4 heteroatoms selected from the group:  
25 pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl,  
pyrazinyl, piperazinyl, piperidinyl, imidazolyl,  
imidazolidinyl, indolyl, tetrazolyl, isoxazolyl,  
morpholinyl, oxazolyl, oxazolidinyl,  
tetrahydrofuranyl, thiadiazinyl, thiadiazolyl,  
30 thiazolyl, triazinyl, triazolyl, benzimidazolyl,  
1*H*-indazolyl, benzofuranyl, benzothiofuranyl,  
benztetrazolyl, benzotriazolyl, benzisoxazolyl,  
benzoxazolyl, oxindolyl, benzoxazolinyl,  
benzthiazolyl, benzisothiazolyl, isatinoyl,  
35 isoquinolinyl, octahydroisoquinolinyl,  
tetrahydroisoquinolinyl, tetrahydroquinolinyl,  
isoxazolopyridinyl, quinazolinyl, quinolinyl,  
isothiazolopyridinyl, thiazolopyridinyl,  
oxazolopyridinyl, imidazolopyridinyl, and  
40 pyrazolopyridinyl; and substituted with 0-3 R<sup>1c</sup>;

5

R<sup>1b</sup> is H,

C<sub>1</sub>-C<sub>4</sub> alkyl substituted with 0-3 R<sup>1c</sup>,

C<sub>2</sub>-C<sub>4</sub> alkenyl substituted with 0-3 R<sup>1c</sup>,

C<sub>2</sub>-C<sub>4</sub> alkynyl substituted with 0-3 R<sup>1c</sup>,

10 C<sub>3</sub>-C<sub>6</sub> cycloalkyl substituted with 0-5 R<sup>1c</sup>,

C<sub>3</sub>-C<sub>6</sub> carbocycle substituted with 0-5 R<sup>1c</sup>,

aryl substituted with 0-5 R<sup>1c</sup>, or

5-6 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group:

15 pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl,

pyrazinyl, piperazinyl, piperidinyl, imidazolyl,

imidazolidinyl, indolyl, tetrazolyl, isoxazolyl,

morpholinyl, oxazolyl, oxazolidinyl,

tetrahydrofuranlyl, thiadiazinyl, thiadiazolyl,

20 thiazolyl, triazinyl, and triazolyl; said

heterocyclic group substituted with 0-3 R<sup>1c</sup>;

R<sup>1c</sup> is selected at each occurrence from: C<sub>1</sub>-C<sub>4</sub> alkyl, Cl,

F, Br, I, OH, C<sub>1</sub>-C<sub>4</sub> alkoxy, -CN, -NO<sub>2</sub>, C(O)OR<sup>1d</sup>,

25 NR<sup>1d</sup>R<sup>1d</sup>, CF<sub>3</sub>, and OCF<sub>3</sub>;

R<sup>1d</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sup>2</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

30

R<sup>3</sup> is selected from the group: H,

C<sub>1</sub>-C<sub>6</sub> alkyl substituted with 0-4 R<sup>3a</sup>,

C<sub>2</sub>-C<sub>6</sub> alkenyl substituted with 0-4 R<sup>3a</sup>,

C<sub>2</sub>-C<sub>6</sub> alkynyl substituted with 0-4 R<sup>3a</sup>,

35 -(CH<sub>2</sub>)<sub>q</sub>- C<sub>3</sub>-C<sub>6</sub> cycloalkyl substituted with 0-4 R<sup>3b</sup>,

-(CH<sub>2</sub>)<sub>q</sub>-aryl substituted with 0-5 R<sup>3b</sup>, and

-(CH<sub>2</sub>)<sub>q</sub>-5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: pyridinyl, furanyl, thienyl, pyrrolyl,

5           pyrazolyl, pyrazinyl, piperazinyl, piperidinyl,  
imidazolyl, imidazolidinyl, indolyl, tetrazolyl,  
isoxazolyl, morpholinyl, oxazolyl, oxazolidinyl,  
tetrahydrofuranyl, thiadiazinyl, thiadiazolyl,  
thiazolyl, triazinyl, triazolyl, benzimidazolyl,  
10       1H-indazolyl, benzofuranyl, benzothiofuranyl,  
benztetrazolyl, benzotriazolyl, benzisoxazolyl,  
benzoxazolyl, oxindolyl, benzoxazolinyl,  
benzthiazolyl, benzisothiazolyl, isatinoyl,  
isoquinolinyl, octahydroisoquinolinyl,  
15       tetrahydroisoquinolinyl, tetrahydroquinolinyl,  
isoxazolopyridinyl, quinazolinyl, quinolinyl,  
isothiazolopyridinyl, thiazolopyridinyl,  
oxazolopyridinyl, imidazolopyridinyl, and  
pyrazolopyridinyl; and said heterocyclic group is  
20       substituted with 0-2 R<sup>3b</sup>;

R<sup>3a</sup> is selected from the group: -CO<sub>2</sub>R<sup>11</sup>, -NR<sup>11</sup>R<sup>11</sup>, -OR<sup>11</sup>,  
-SR<sup>11</sup>, -C(=NH)NH<sub>2</sub>, and aryl substituted with R<sup>10b</sup>;

25   R<sup>3b</sup> is selected from the group: -CO<sub>2</sub>H, - NH<sub>2</sub>, -OH, -SH, and  
-C(=NH)NH<sub>2</sub>;

R<sup>3c</sup> is, at each occurrence, independently selected from: H,  
C<sub>1</sub>-C<sub>6</sub> alkyl, -OH, and OR<sup>3d</sup>;

30   R<sup>3d</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl,  
-(CH<sub>2</sub>)<sub>q</sub>- C<sub>3</sub>-C<sub>6</sub> cycloalkyl, -(CH<sub>2</sub>)<sub>q</sub>-aryl, or  
-(CH<sub>2</sub>)<sub>q</sub>-(5-10 membered heterocyclic group), wherein  
said heterocyclic group consists of carbon atoms  
35       and 1-4 heteroatoms selected from the group: O,  
S, and N;

R<sup>4</sup> is selected from the group: H, C<sub>1</sub>-C<sub>6</sub> alkyl, phenyl,  
phenylmethyl-, phenylethyl-, C<sub>3</sub>-C<sub>6</sub> cycloalkyl,  
40       C<sub>3</sub>-C<sub>6</sub> cycloalkylmethyl-, and C<sub>3</sub>-C<sub>6</sub> cycloalkylethyl-;



5

R<sup>9</sup> is selected from -S(=O)<sub>2</sub>R<sup>9a</sup> and -C(=O)R<sup>9a</sup>;

R<sup>9a</sup> is selected from the group:

phenyl substituted with 0-3 R<sup>9c</sup>,  
10 naphthyl substituted with 0-3 R<sup>9c</sup>, and  
5-14 membered heterocyclic group consisting of carbon  
atoms and 1-4 heteroatoms selected from the  
group: pyridinyl, furanyl, thienyl, pyrrolyl,  
pyrazolyl, pyrazinyl, piperazinyl, piperidinyl,  
15 imidazolyl, imidazolidinyl, indolyl, tetrazolyl,  
isoxazolyl, morpholinyl, oxazolyl, oxazolidinyl,  
tetrahydrofuranyl, thiadiazinyl, thiadiazolyl,  
thiazolyl, triazinyl, triazolyl, benzimidazolyl,  
1*H*-indazolyl, benzofuranyl, benzothiofuranyl,  
20 benztetrazolyl, benzotriazolyl, benzisoxazolyl,  
benzoxazolyl, oxindolyl, benzoxazolinyl,  
benzthiazolyl, benzisothiazolyl, isatinoyl,  
isoquinolinyl, octahydroisoquinolinyl,  
tetrahydroisoquinolinyl, tetrahydroquinolinyl,  
25 isoxazolopyridinyl, quinazolinyl, quinolinyl,  
isothiazolopyridinyl, thiazolopyridinyl,  
oxazolopyridinyl, imidazolopyridinyl, and  
pyrazolopyridinyl; and said heterocyclic group is  
substituted with 0-3 R<sup>9c</sup>;

30

R<sup>9c</sup> is selected at each occurrence from the group:

CF<sub>3</sub>, OCF<sub>3</sub>, Cl, F, Br, I, =O, OH, phenyl, C(O)OR<sup>11</sup>, NH<sub>2</sub>,  
NH(CH<sub>3</sub>), N(CH<sub>3</sub>)<sub>2</sub>, -CN, NO<sub>2</sub>;  
C<sub>1</sub>-C<sub>4</sub> alkyl substituted with 0-3 R<sup>9d</sup>,  
35 C<sub>1</sub>-C<sub>4</sub> alkoxy substituted with 0-3 R<sup>9d</sup>,  
C<sub>3</sub>-C<sub>6</sub> cycloalkyl substituted with 0-3 R<sup>9d</sup>,  
aryl substituted with 0-5 R<sup>9d</sup>, and  
5-6 membered heterocyclic group consisting of carbon  
atoms and 1-4 heteroatoms selected from the  
40 group: pyridinyl, furanyl, thienyl, pyrrolyl,

5           pyrazolyl, pyrazinyl, piperazinyl, piperidinyl,  
imidazolyl, imidazolidinyl, indolyl, tetrazolyl,  
isoxazolyl, morpholinyl, oxazolyl, oxazolidinyl,  
tetrahydrofuranyl, thiadiazinyl, thiadiazolyl,  
thiazolyl, triazinyl, and triazolyl; said  
10           heterocyclic group is substituted with 0-4 R<sup>9d</sup>;

R<sup>9d</sup> is selected at each occurrence from the group:

          C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CF<sub>3</sub>, OCF<sub>3</sub>, Cl, F, Br, I, =O,  
          OH, phenyl, C(O)OR<sup>11</sup>, NH<sub>2</sub>, NH(CH<sub>3</sub>), N(CH<sub>3</sub>)<sub>2</sub>, -CN, and  
15           NO<sub>2</sub>;

p is 1 or 2; and

q, at each occurrence, is independently 0, 1 or 2.  
20

[6] In a further even more preferred embodiment, the  
present invention provides novel compounds of Formula III,  
wherein:

25   X is -C(=O)-;

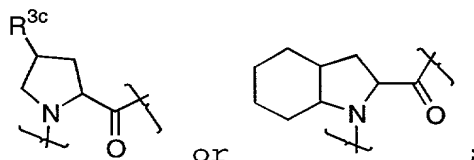
Y is -S(=O)<sub>2</sub>-;

Z is selected from the group:

30   methyl, ethyl, propyl, trifluoromethyl,  
phenyl, benzyl, 4-phenyl-phenyl, 4-NCS-phenyl,  
2-fluorophenyl-, 3-fluorophenyl-, 4-fluorophenyl-,  
2-chlorophenyl-, 3-chlorophenyl-, 4-chlorophenyl-,  
2-cyanophenyl-, 3-cyanophenyl-, 4-cyanophenyl-,  
35   2-nitrophenyl-, 3-nitrophenyl-, 4-nitrophenyl-,  
2-CF<sub>3</sub>SO<sub>2</sub>-phenyl-, 3-CF<sub>3</sub>SO<sub>2</sub>-phenyl-, 4-CF<sub>3</sub>SO<sub>2</sub>-phenyl-,  
2-CF<sub>3</sub>-phenyl-, 3-CF<sub>3</sub>-phenyl-, 4-CF<sub>3</sub>-phenyl-,  
3-NO<sub>2</sub>-4-Cl-phenyl-, 3-Cl-4-CH<sub>3</sub>-phenyl-,  
2-Cl-5-CF<sub>3</sub>-phenyl-, 2-Cl-5-CO<sub>2</sub>H-phenyl-,  
40   3-NO<sub>2</sub>-4-CH<sub>3</sub>-phenyl-, 3-Cl-5-NH<sub>2</sub>SO<sub>2</sub>-phenyl-,  
3,5-diCF<sub>3</sub>-phenyl-, 3,4-diCF<sub>3</sub>-phenyl-,

5 3,5-diCl-phenyl-, 2,5-diCl-phenyl-, 3,4-diCl-phenyl-,  
 3,5-diF-phenyl-, 2,5-diF-phenyl-, 3,4-diF-phenyl-,  
 2-F-4-Cl-5-CO<sub>2</sub>H-phenyl-, 2,4-diCl-5-CO<sub>2</sub>H-phenyl-,  
 2,4-diCl-5-CH<sub>3</sub>CO<sub>2</sub>-phenyl-, 2,4-diCl-5-CH<sub>3</sub>-phenyl-,  
 2-OH-3,5-diCl-phenyl-, 2,4,5-triCl-phenyl-,  
 10 3,5-diCl-4-(4-NO<sub>2</sub>phenyl)phenyl-,  
 2-Cl-5-benzylNHCO-phenyl-, 2-Cl-5-CF<sub>3</sub>CH<sub>2</sub>NHCO-phenyl-,  
 2-Cl-5-cyclopropylmethylNHCO-phenyl-,  
 2-Cl-4-CH<sub>3</sub>CONH-phenyl-, 3-Cl-5-(phenylCONHSO<sub>2</sub>)-phenyl-,  
 3-Cl-5-CH<sub>3</sub>CONH-phenyl-, 5-ethoxy-benzothiazol-2-yl,  
 15 naphth-2-yl, (CH<sub>3</sub>CONH)thiadiazolyl-,  
 (s-butylCONH)thiadiazolyl-, (n-pentylCONH)thiadiazolyl-,  
 (phenylCONH)thiadiazolyl-, and  
 (3-ClphenylCONH)thiadiazolyl-;

20 A<sup>2</sup> is a bond, Ala, Arg, Asn, Asp, Aze, Cha, Cys, Dpa, Gln,  
 Glu, Gly, His, Hyp, Ile, Irg, Leu, Lys, Met, Orn, Phe,  
 Phe(4-fluoro), Pro, Sar, Ser, Thr, Trp, Tyr, Val;



25

A<sup>3</sup> is a bond, Ala, Arg, Asn, Asp, Aze, Cha, Cys, Dpa, Gln,  
 Glu, Gly, His, Hyp, Ile, Irg, Leu, Lys, Met, Orn, Phe,  
 Phe(4-fluoro), Pro, Sar, Ser, Thr, Trp, Tyr, or Val;

30 A<sup>3</sup> is a bond, Ala, Arg, Asn, Asp, Aze, Cha, Cys, Dpa, Gln,  
 Glu, Gly, His, Hyp, Ile, Irg, Leu, Lys, Met, Orn, Phe,  
 Phe(4-fluoro), Pro, Sar, Ser, Thr, Trp, Tyr, or Val;

R<sup>1</sup> is selected from the group:

35 -CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CH(CH<sub>3</sub>)<sub>2</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>,  
 -CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, -CH<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>,  
 -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>,  
 -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>,

5        $-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ,  
           $-\text{CH}_2\text{CF}_3$ ,  $-\text{CH}_2\text{CH}_2\text{CF}_3$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CF}_3$ ,  
           $-\text{CH}_2\text{CHF}_2$ ,  $-\text{CH}_2\text{CH}_2\text{CHF}_2$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CHF}_2$ ,  
           $-\text{CH}=\text{CH}_2$ ,  $-\text{CH}_2\text{CH}=\text{CH}_2$ ,  $-\text{CH}=\text{CHCH}_3$ , *cis*- $\text{CH}_2\text{CH}=\text{CH}(\text{CH}_3)$ ,  
          *trans*- $\text{CH}_2\text{CH}=\text{CH}(\text{CH}_3)$ ,  $-\text{CH}_2\text{CH}_2\text{CH}=\text{CH}$ ,  $-\text{CH}_2\text{CH}=\text{C}(\text{CH}_3)_2$ ,  
 10        $-\text{CH}_2\text{CH}_2\text{CH}=\text{C}(\text{CH}_3)_2$ ,  
           $-\text{CH}_2\text{CO}_2\text{H}$ ,  $-\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$ ,  $-\text{CH}_2\text{CO}_2\text{C}(\text{CH}_3)_3$ ,  
           $-\text{CH}_2\text{CH}_2\text{CO}_2\text{C}(\text{CH}_3)_3$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$ ,  
          phenyl, benzyl, phenethyl, phenpropyl, phenbutyl,  
          (2-methylphenyl)ethyl-, (3-methylphenyl)ethyl-,  
 15       (4-methylphenyl)ethyl-, (4-ethylphenyl)ethyl-,  
          (4-*i*-propylphenyl)ethyl-, (4-*t*-butylphenyl)ethyl-,  
          (4-hydroxyphenyl)ethyl-, (4-phenyl-phenyl)ethyl-,  
          (4-phenoxy-phenyl)ethyl-, (4-cyclohexyl-phenyl)ethyl-,  
          (4-cyclopropyl-phenyl)ethyl-,  
 20       (2,5-dimethylphenyl)ethyl-,  
          (2,4-dimethylphenyl)ethyl-, (2,6-difluorophenyl)ethyl-,  
          (4-cyclopentyl-phenyl)ethyl-,  
          (4-cyclobutyl-phenyl)ethyl-,  
          (2-trifluoromethylphenyl)ethyl-,  
 25       (3-trifluoromethylphenyl)ethyl-,  
          (4-trifluoromethylphenyl)ethyl-,  
          (2-fluorophenyl)ethyl-, (3-fluorophenyl)ethyl-,  
          (4-fluorophenyl)ethyl-, (2-chlorophenyl)ethyl-,  
          (3-chlorophenyl)ethyl-, (4-chlorophenyl)ethyl-,  
 30       (2-bromophenyl)ethyl-, (3-bromophenyl)ethyl-,  
          (4-bromophenyl)ethyl-,  
          (2,3,4,5,6-pentafluorophenyl)ethyl-,  
          (naphth-2-yl)ethyl, (cyclobutyl)methyl,  
          (cyclobutyl)ethyl, (cyclobutyl)propyl, cyclopropyl,  
 35       cyclobutyl, cyclopentyl, and cyclohexyl;

$\text{R}^2$  is H, methyl or ethyl;

40        $\text{R}^{3c}$  is H, methyl, ethyl, -OH, methoxy, ethoxy, propoxy,  
          phenoxy, or benzyloxy; and

$\text{R}^9$  is selected from:

5        2-pyrazinyl-carbonyl-,  
          4-(N-pyrrolyl)phenyl-carbonyl-,  
          5-(4-chlorophenyl)furan-2-yl-carbonyl-,  
          1-anthracenyl-carbonyl-,  
          7-nitro-anthracen-1-yl-carbonyl-,  
 10       (3-phenyl-2-cyanomethoxyphenyl)carbonyl-,  
          5-(2-Cl-3-CF<sub>3</sub>-phenyl)-furan-2-yl-carbonyl-,  
          5-(4-Cl-phenyl)-furan-2-yl-carbonyl-,  
          5-(pyrid-2-yl)-thiophen-2-yl-carbonyl-,  
          (2-methoxyphenyl)ethylcarbonyl-,  
 15       (3-benzopyrrolyl)ethylcarbonyl-,  
          (N-phenyl-5-propyl-imidazol-4-yl)-carbonyl-,  
          1-naphthyl-sulphonyl-, and  
          5-(isoxazol-2-yl)thiophen-2-yl-sulphonyl-.

20       [7] In most preferred embodiment, the compound of Formula  
          (I) is selected from the group:

         N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-  
          L-alanyl-2-oxo-(3 S)-3-amino pentanoylglycine;

25       (3S)-2-oxo-3-{[N-(2-pyrazinylcarbonyl)-L-leucyl-L-  
          isoleucyl-3-cyclohexyl-L-alanyl]amino}-N-(2H-tetrazol-5-  
          ylmethyl) pentanamide;

30       2-oxo-3-[N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-  
          cyclohexylalanyl]amino]-N-(sulfomethyl)pentanamide;

         N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-  
          cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(2-nitrophenyl)  
 35       sulfonyl]glycinamide;

         N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-  
          cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-(methylsulfonyl)  
          glycineamide;

40

- 5 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(phenylmethyl)sulfonyl]glycinamide;
- 10 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-(phenylsulfonyl)glycinamide;
- 15 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(trifluoromethyl)sulfonyl]glycinamide;
- 20 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(2-nitrophenyl)sulfonyl]glycinamide;
- 25 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(4-fluorophenyl)sulfonyl]glycinamide;
- 30 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-(3 S)-3-amino pentanoyl-N-[(3-fluorophenyl)sulfonyl]glycinamide;
- 35 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(2-fluorophenyl) sulfonyl]glycinamide;
- 40 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(4-chlorophenyl) sulfonyl]glycinamide;

- 5 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(3-chlorophenyl) sulfonyl]glycinamide;
- 10 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[[4-(thionitroso) phenyl]sulfonyl]glycinamide;
- 15 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[[4-[(trifluoromethyl) sulfonyl]phenyl]sulfonyl]glycinamide;
- 20 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[[4-(trifluoromethyl)phenyl]sulfonyl]glycinamide;
- 25 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(3-chloro-4-methylphenyl) sulfonyl]glycinamide;
- 30 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(4-chloro-3-nitrophenyl) sulfonyl]glycinamide;
- 35 N-(2-pyrazinylcarbonyl)-L-leucyl-L- isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(3,5-dichlorophenyl) sulfonyl]glycinamide;
- 40 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(4-methyl-3-nitrophenyl) sulfonyl]glycinamide;

- 5 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[[2-chloro-5-(trifluoromethyl)phenyl]sulfonyl]glycinamide;
- 10 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(5-carboxy-2-chlorophenyl)sulfonyl]glycinamide;
- 15 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(2,5-dichlorophenyl)sulfonyl]glycinamide;
- 20 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(3,4-difluorophenyl)sulfonyl]glycinamide;
- 25 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-amino pentanoyl-N-[(2,4,5-trichlorophenyl)-sulfonyl]glycinamide;
- 30 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(5-carboxy-4-chloro-2-fluorophenyl)sulfonyl]glycinamide;
- 35 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[[5-(dimethylamino)-1-naphthalenyl]sulfonyl]glycinamide;
- 40 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-(2-naphthalenylsulfonyl)glycinamide;



- 5 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[(4-(phenyl)phenyl)-sulfonyl]glycinamide;
- 10 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(6-ethoxy-2-benzothiazolyl)sulfonyl]glycinamide;
- 15 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[[2-chloro-5-[(phenylmethyl)amino]carbonyl]phenyl]sulfonyl]glycinamide;
- 20 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[2-chloro-5-[(2-trifluoroethyl)amino]carbonyl]phenyl]sulfonyl]glycinamide;
- 25 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[2-chloro-5-[(cyclopropylmethyl)amino]carbonyl]phenyl]sulfonyl]glycinamide;
- 30 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[3-nitro-4-(2-pyrimidinylthio)phenyl]sulfonyl]glycinamide;
- 35 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[3-chloro-4-(2-benzoxazolylthio)phenyl]sulfonyl]glycinamide;
- 40 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[3,5-dichloro-4-(4-nitrophenoxy)phenyl]sulfonyl]glycinamide;

- 5 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3 S)-3-amino pentanoyl-N-[[5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl]glycinamide;
- 10 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3 S)-3-amino pentanoyl-N-[(3-cyanophenyl)sulfonyl]glycinamide;
- 15 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3 S)-3-amino pentanoyl-N-[[3-(aminosulfonyl)-5-chlorophenyl]sulfonyl]glycinamide;
- 20 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-amino pentanoyl-N-[[3,5-bis(trifluoromethyl)phenyl]sulfonyl]glycinamide;
- 25 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[4-[5-[3-(4-chlorophenyl)-3-oxo-1-propenyl]-2-furanyl]phenyl]sulfonyl]glycinamide;
- 30 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[3-[[2,2,2-trifluoroethyl)amino]carbonyl]phenyl]sulfonyl]glycinamide;
- 35 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[3-[(benzoylamino)sulfonyl]-5-chlorophenyl]sulfonyl]glycinamide;
- 40 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoylglycine;

- 5 (3S)-5,5-difluoro-2-oxo-3-[[N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl]amino]-N-(2H-tetrazol-5-ylmethyl)pentanamide;
- 10 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[(3,5-dichlorophenyl)sulfonyl]glycinamide;
- 15 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[(3-chlorophenyl)sulfonyl]glycinamide;
- 20 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl]glycinamide;
- 25 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-(3-aminosulfonyl-5-chlorophenyl)sulfonyl]glycinamide;
- 30 (3S)-5,5,5-trifluoro-2-oxo-3-[[N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl]amino]-N-(2H-tetrazol-5-ylmethyl)pentanamide;
- 35 N-[4-sec-butyl-15-{{(3-chloro-5-{{(3,3,3-trifluoropropanoyl)amino}sulfonyl}phenyl)sulfonyl}amino}-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;
- 40 N-[4-sec-butyl-15-[(3-chloro-5-[(hexanoylamino)sulfonyl]phenyl)sulfonyl]amino]-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;
- 40 N-[15-[(1,1'-biphenyl)-3-ylsulfonyl]amino]-4-sec-butyl-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-2,5,8,11,12,15-

5 hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-  
pyrazinecarboxamide;

*N*-(4-*sec*-butyl-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-15-  
{[(4'-methoxy[1,1'-biphenyl]-4-yl)sulfonyl]amino}-  
10 2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl)-2-  
pyrazinecarboxamide;

*N*-(4-*sec*-butyl-7-(cyclohexylmethyl)-15-{{(3',5'-  
dichloro[1,1'-biphenyl]-4-yl)sulfonyl]amino}-10-ethyl-1-  
15 isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-  
1-yl)-2-pyrazinecarboxamide;

*N*-[4-*sec*-butyl-15-{{(4'-chloro[1,1'-biphenyl]-3-  
yl)sulfonyl]amino}-7-(cyclohexylmethyl)-10-(2,2-  
20 difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-  
tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

*N*-[4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-  
1-isobutyl-15-({[3-(2-methylphenoxy)phenyl]sulfonyl}amino)-  
25 2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-  
pyrazinecarboxamide;

*N*-[4-*sec*-butyl-15-({[3-(2-  
chlorophenoxy)phenyl]sulfonyl}amino)-7-(cyclohexylmethyl)-  
30 10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-  
3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

(3*S*,6*S*,9*S*,12*S*)-9-(cyclohexylmethyl)-12-(2,2-difluoroethyl)-  
3-isobutyl-6-[(1*R*)-1-methylpropyl]-1,4,7,10,13-pentaoxo-1-  
35 (2-pyrazinyl)-2,5,8,11-tetraazatetradecan-14-oic acid;

*N*-(4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-  
1-isobutyl-15-{{(4'-methyl[1,1'-biphenyl]-3-  
yl)sulfonyl]amino}-2,5,8,11,12,15-hexaoxo-3,6,9,13-  
40 tetraazapentadec-1-yl)-2-pyrazinecarboxamide;

- 5 *N*-[15-({[3',5'-bis(trifluoromethyl)[1,1'-biphenyl]-3-yl)sulfonyl}amino)-4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;
- 10 *N*-[4-*sec*-butyl-15-[(5-[(4-cyanobenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl]amino]-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;
- 15 *N*-[4-*sec*-butyl-15-[(5-[(2-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl]amino]-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;
- 20 *N*-{4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-15-[(5-[(4-methoxybenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl]amino}-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl}-2-pyrazinecarboxamide;
- 25 *N*-{4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-15-[(5-[(3-methoxybenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl]amino}-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl}-2-pyrazinecarboxamide;
- 30 *N*-{4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-15-[(5-[(3,5-dimethylbenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl]amino}-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl}-2-pyrazinecarboxamide;
- 35 *N*-(4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-15-[(3-phenoxyphenyl)sulfonyl]amino)-3,6,9,13-tetraazapentadec-1-yl)-2-pyrazinecarboxamide;
- 40 6-*sec*-butyl-9-(cyclohexylmethyl)-12-ethyl-3-isobutyl-1,4,7,10,13-pentaoxo-1-(2-pyrazinyl)-2,5,8,11-tetraazatetradecan-14-oic acid;

5 *N*-{4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-  
1-isobutyl-15-[(5-[(3-methylbutanoyl)amino]-1,3,4-  
thiadiazol-2-yl)sulfonyl]amino}-2,5,8,11,12,15-hexaoxo-  
3,6,9,13-tetraazapentadec-1-yl}-2-pyrazinecarboxamide;

10 *N*-[4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-  
15-([5-(hexanoylamino)-1,3,4-thiadiazol-2-  
yl)sulfonyl]amino)-1-isobutyl-2,5,8,11,12,15-hexaoxo-  
3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

15 methyl (3*S*,6*S*,9*S*,12*S*)-9-(cyclohexylmethyl)-12-(2,2-  
difluoroethyl)-3-isobutyl-6-[(1*R*)-1-methylpropyl]-  
1,4,7,10,13,14-hexaoxo-1-(2-pyrazinyl)-2,5,8,11,15-  
pentaazaheptadecan-17-oate;

20 *N*-[4-*sec*-butyl-15-[(3-chloro-5-[(3-  
chlorobenzoyl)amino]sulfonyl]phenyl)sulfonyl]amino}-7-  
(cyclohexylmethyl)-10-ethyl-1-isobutyl-2,5,8,11,12,15-  
hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-  
25 pyrazinecarboxamide;

*N*-[4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-  
1-isobutyl-2,5,8,11,12,15-hexaoxo-15-([4'-  
(trifluoromethyl)[1,1'-biphenyl]-3-yl)sulfonyl]amino)-  
30 3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

*N*-[15-([1,1'-biphenyl]-3-ylsulfonyl)amino]-4-*sec*-butyl-7-  
(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-  
2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-  
35 pyrazinecarboxamide;

*N*-[4-*sec*-butyl-15-[(5-[(4-*tert*-butylbenzoyl)amino]-1,3,4-  
thiadiazol-2-yl)sulfonyl]amino]-7-(cyclohexylmethyl)-10-  
(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-  
40 3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

5 *N*-[4-*sec*-butyl-15-{{(3-chloro-5-{{(3-methylbutanoyl)amino}sulfonyl}phenyl)sulfonyl}amino}-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;  
 10  
*N*-{(1*S*,4*S*,7*S*,10*S*)-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-14-[4-(4-methoxyphenyl)-5-(trifluoromethyl)-4*H*-1,2,4-triazol-3-yl]-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-tetraazatetradec-1-yl}-2-pyrazinecarboxamide;  
 15  
*N*-{4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-15-[(5-[(4-ethylbenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl]amino}-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl}-2-pyrazinecarboxamide;  
 20  
*N*-[4-*sec*-butyl-15-[(5-[(4-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl]amino]-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;  
 25  
*N*-[4-*sec*-butyl-7-(cyclohexylmethyl)-15-[(5-[(3,5-difluorobenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl]amino]-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;  
 30  
*N*-[4-*sec*-butyl-15-[(5-[(3-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl]amino]-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;  
 35  
*N*-{(1*S*,4*S*,7*S*,10*S*)-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-tetraazahexadec-15-en-1-yl}-2-pyrazinecarboxamide;  
 40

- 5 *N*-{(1*S*,4*S*,7*S*,10*S*)-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-tetraazahexadec-15-yn-1-yl}-2-pyrazinecarboxamide;
- 10 *tert*-butyl (3*S*,6*S*,9*S*,12*S*)-9-(cyclohexylmethyl)-12-ethyl-3-isobutyl-6-[(1*R*)-1-methylpropyl]-1,4,7,10,13,14-hexaoxo-1-(2-pyrazinyl)-2,5,8,11,15-pentaazaheptadecan-17-oate;
- 15 *N*-{(1*S*,4*S*,7*S*,10*S*)-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-14-phenyl-3,6,9,13-tetraazatetradec-1-yl}-2-pyrazinecarboxamide
- 20 *N*-((1*S*)-1-{[(1*S*,2*R*)-1-{[(1*S*)-1-(cyclohexylmethyl)-2-{[(1*S*)-1-ethyl-2,3-dioxo-3-(1-pyrrolidinyl)propyl]amino}-2-oxoethyl)amino]carbonyl}-2-methylbutyl)amino]carbonyl}-3-methylbutyl)-2-pyrazinecarboxamide;
- 25 *N*-{(1*S*,4*S*,7*S*,10*S*)-7-(cyclohexylmethyl)-10-ethyl-15,15,15-trifluoro-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-tetraazapentadec-1-yl}-2-pyrazinecarboxamide;
- 30 *N*-{(1*S*,4*S*,7*S*,10*S*)-15-amino-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl}-2-pyrazinecarboxamide;
- 35 (3*S*,6*S*,9*S*,12*S*,16*S*)-9-(cyclohexylmethyl)-12-ethyl-3-isobutyl-16-methyl-6-[(1*R*)-1-methylpropyl]-1,4,7,10,13,14-hexaoxo-1-(2-pyrazinyl)-2,5,8,11,15-pentaazaheptadecan-17-oic acid;
- N*-[9-*sec*-butyl-6-(cyclohexylmethyl)-3-ethyl-12-isobutyl-2,5,8,11,14-pentaoxo-14-(2-pyrazinyl)-4,7,10,13-tetraazatetradec-1-anoyl]aspartic acid;
- 40 (3*S*,6*S*,9*S*,12*S*)-9-(cyclohexylmethyl)-12-ethyl-3-isobutyl-6-[(1*R*)-1-methylpropyl]-1,4,7,10,13,14-hexaoxo-1-(2-pyrazinyl)-2,5,8,11,15-pentaazaoctadecan-18-oic acid;



5

1,1-dimethylethyl N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoylglycine;

10 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoylglycine;

(4R)-1-[N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl]-N-  
15 [(1S)-1-(2,2-difluoroethyl)-2,3-dioxo-3-[(2H)-tetrazol-5-ylmethyl]amino]propyl]-4-(phenylmethoxy)-L-prolinamide;

(4R)-N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-N-[(1S)-  
1-(2,2-difluoroethyl)-3-methoxy-2,3-dioxopropyl]-4-  
20 (phenylmethoxy)-L-prolinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[(3-chlorophenyl)sulfonyl]glycinamide;

25 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[(5-carboxy-2-chlorophenyl)sulfonyl]glycinamide;

30 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[(5-acetyl amino)1,3,4-thiadiazol-2-yl)sulfonyl]glycinamide;

35 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[3,5-dichlorophenyl)sulfonyl]glycinamide;

40 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-

- 5 aminopentanoyl N-(4-methyl-3-nitrophenyl)sulfonyl]-  
glycinamide;
- N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-  
(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-  
10 aminopentanoyl N-(3-carboxyl-4-chloro-2-  
fluorophenyl)sulfonyl]-glycinamide;
- N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-  
(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-  
15 aminopentanoyl N-[(3-chloro-4-acetylamino)phenyl]sulfonyl]-  
glycinamide;
- N-((1S)-1-{[(1S,2R)-1-{(2S,4R)-2-({[(1S)-3-({2-[(3-  
20 [(benzoylamino)sulfonyl]-5-chlorophenyl)sulfonyl]amino)-2-  
oxoethyl}amino)-1-(2,2-difluoroethyl)-2,3-  
dioxopropyl]amino}carbonyl)-4-  
(benzyloxy)pyrrolidinyl]carbonyl}-2-  
methylbutyl)amino]carbonyl}-3-methylbutyl)-2-  
pyrazinecarboxamide;
- 25 *tert*-butyl {[(3S)-3-[(2S,4R)-4-(benzyloxy)-1-[(2S)-3-  
methyl-2-[(2S)-3-methyl-2-[(2-  
pyrazinylcarbonyl]amino]butanoyl]amino)butanoyl]pyrrolidiny  
l]carbonyl]amino]-5,5-difluoro-2-  
30 oxopentanoyl]amino)acetate;
- N-((1S)-1-{[(1S,2R)-1-{(2S,4R)-4-(benzyloxy)-2-({[(1S)-3-  
[(2-[(3-chloro-4-methylphenyl)sulfonyl]amino)-2-  
oxoethyl]amino)-1-(2,2-difluoroethyl)-2,3-  
35 dioxopropyl]amino}carbonyl)pyrrolidinyl]carbonyl}-2-  
methylbutyl)amino]carbonyl}-3-methylbutyl)-2-  
pyrazinecarboxamide;
- N-((1S)-1-{[(1S,2R)-1-{(2S,4R)-4-(benzyloxy)-2-({[(1S)-3-  
40 {2-[(5-[(3-chlorobenzoyl]amino)-1,3,4-thiadiazol-2-  
yl]sulfonyl]amino)-2-oxoethyl}amino)-1-(2,2-difluoroethyl)-  
2,3-dioxopropyl]amino}carbonyl)pyrrolidinyl]carbonyl}-2-

5 methylbutyl) amino] carbonyl} -3-methylbutyl) -2-  
pyrazinecarboxamide;

methyl ({(3*S*)-3-[( {(2*S*,4*R*)-4-(benzyloxy)-1-[(2*S*,3*R*)-3-  
methyl-2-({(2*S*)-4-methyl-2-[(2-  
10 pyrazinylcarbonyl) amino] pentanoyl} amino) pentanoyl] pyrrolidi  
nyl} carbonyl) amino] -5,5-difluoro-2-  
oxopentanoyl} amino) acetate;

*N*-{(1*S*)-1-[( {(1*S*,2*R*)-1-[( {(2*S*,4*R*)-4-(benzyloxy)-2-[( {(1*S*)-3-  
15 [(2-[( (2,4-dichloro-5-methylphenyl) sulfonyl] amino)-2-  
oxoethyl) amino] -1-(2,2-difluoroethyl)-2,3-  
dioxopropyl} amino) carbonyl] pyrrolidinyl} carbonyl} -2-  
methylbutyl) amino] carbonyl} -3-methylbutyl) -2-  
pyrazinecarboxamide;

20 *N*-[(1*S*)-1-[( {(1*S*,2*R*)-1-[( {(2*S*,4*R*)-4-(benzyloxy)-2-[( {(1*S*)-1-  
(2,2-difluoroethyl)-3-[(2-[( (3,4-  
difluorophenyl) sulfonyl] amino)-2-oxoethyl) amino] -2,3-  
dioxopropyl} amino) carbonyl] pyrrolidinyl} carbonyl) -2-  
25 methylbutyl] amino} carbonyl} -3-methylbutyl] -2-  
pyrazinecarboxamide;

methyl 5-([( {(3*S*)-3-[( {(2*S*,4*R*)-4-(benzyloxy)-1-[(2*S*,3*R*)-3-  
methyl-2-({(2*S*)-4-methyl-2-[(2-  
30 pyrazinylcarbonyl) amino] pentanoyl} amino) pentanoyl] pyrrolidi  
nyl} carbonyl) amino] -5,5-difluoro-2-  
oxopentanoyl} amino) acetyl] amino) sulfonyl) -2,4-  
dichlorobenzoate;

35 *N*-{(1*S*)-1-[( {(1*S*,2*R*)-1-[( {(2*S*,4*R*)-4-(benzyloxy)-2-[( {(1*S*)-1-  
(2,2-difluoroethyl)-3-[(2-[( (4-(3,5-dimethyl-1-  
piperidinyl)-3-nitrophenyl] sulfonyl} amino)-2-  
oxoethyl] amino)-2,3-  
dioxopropyl} amino] carbonyl] pyrrolidinyl} carbonyl] -2-  
40 methylbutyl} amino) carbonyl] -3-methylbutyl} -2-  
pyrazinecarboxamide;

5 N-[(1S)-1-({[(1S,2R)-1-({(2S,4R)-4-(benzyloxy)-2-[(1S)-1-(2,2-difluoroethyl)-3-[(2-[(3-nitrophenyl)sulfonyl]amino)-2-oxoethyl]amino)-2,3-dioxopropyl]amino)carbonyl]pyrrolidinyl)carbonyl)-2-methylbutyl]amino)carbonyl)-3-methylbutyl]-2-pyrazinecarboxamide;

N-{(1S)-1-[(1S,2R)-1-[(2S,4R)-4-(benzyloxy)-2-[(1S)-1-(2,2-difluoroethyl)-3-{[2-[(5-(hexanoylamino)-1,3,4-thiadiazol-2-yl]sulfonyl]amino)-2-oxoethyl]amino)-2,3-dioxopropyl]amino]carbonyl]pyrrolidinyl)carbonyl]-2-methylbutyl]amino)carbonyl]-3-methylbutyl}-2-pyrazinecarboxamide;

5-({[(3S)-3-[(2S,4R)-4-(benzyloxy)-1-[(2S,3R)-3-methyl-2-[(2S)-4-methyl-2-[(2-pyrazinylcarbonyl)amino]pentanoyl]amino)pentanoyl]pyrrolidinyl)carbonyl]amino)-5,5-difluoro-2-oxopentanoyl]amino)acetyl]amino)sulfonyl)-2,4-dichlorobenzoic acid;

25 N-[[5-(4-chlorophenyl)-2-furanyl]carbonyl]-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoylglycine;

30 N-[[5-(4-chlorophenyl)-2-furanyl]carbonyl]-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(trifluoromethyl)sulfonyl]glycinamide;

35 N-[[5-(4-chlorophenyl)-2-furanyl]carbonyl]-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(3,5-dichlorophenyl)sulfonyl]glycinamide;

40 N-[[5-(4-chlorophenyl)-2-furanyl]carbonyl]-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(3-nitrophenyl)sulfonyl]glycinamide;

5 (4R)-1-[[5-(4-chlorophenyl)-2-furanyl]carbonyl-L-isoleucyl-N-[(1S)-1-(2,2-difluoroethyl)-2,3-dioxo-3-[(2H-tetrazol-5-ylmethyl)amino]propyl]-4-(phenylmethoxy)-L-prolinamide;

(2S,4R)-4-(benzyloxy)-N-{(1S)-1-(2,2-difluoroethyl)-2,3-dioxo-3-[(2H-tetraazol-5-ylmethyl)amino]propyl}-1-((2S,3R)-3-methyl-2-{[(9-oxo-9H-fluoren-1-yl)carbonyl]amino}pentanoyl)-2-pyrrolidinecarboxamide;

10 tert-butyl {[ (3S)-3-({[(2S,4R)-4-(benzyloxy)-1-((2S,3R)-3-methyl-2-{[(9-oxo-9H-fluoren-1-yl)carbonyl]amino}pentanoyl)pyrrolidinyl]carbonyl}amino)-5,5-difluoro-2-oxopentanoyl]amino}acetate;

15 {[ (3S)-3-({[(2S,4R)-4-(benzyloxy)-1-((2S,3R)-3-methyl-2-{[(9-oxo-9H-fluoren-1-yl)carbonyl]amino}pentanoyl)pyrrolidinyl]carbonyl}amino)-5,5-difluoro-2-oxopentanoyl]amino}acetic acid;

20 (2S,4R)-N-[(1S)-3-{[2-({[5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl}amino)-2-oxoethyl]amino}-1-(2,2-difluoroethyl)-2,3-dioxopropyl]-4-(benzyloxy)-1-((2S,3R)-3-methyl-2-{[(9-oxo-9H-fluoren-1-yl)carbonyl]amino}pentanoyl)-2-pyrrolidinecarboxamide;

25 (2S,4R)-4-(benzyloxy)-N-((1S)-1-(2,2-difluoroethyl)-3-{[2-({[5-(hexanoylamino)-1,3,4-thiadiazol-2-yl]sulfonyl}amino)-2-oxoethyl]amino}-2,3-dioxopropyl)-1-((2S,3R)-3-methyl-2-{[(9-oxo-9H-fluoren-1-yl)carbonyl]amino}pentanoyl)-2-pyrrolidinecarboxamide;

30 ((2S,4R)-4-(benzyloxy)-N-[(1S)-3-({2-[(5-(4-chlorobenzoyl)amino)-1,3,4-thiadiazol-2-yl]sulfonyl}amino)-2-oxoethyl]amino)-1-(2,2-difluoroethyl)-2,3-dioxopropyl]-1-((2S,3R)-3-methyl-2-{[(9-oxo-9H-fluoren-1-yl)carbonyl]amino}pentanoyl)-2-pyrrolidinecarboxamide;

35 40

5 (2*S*,4*R*)-4-(benzyloxy)-*N*-[(1*S*)-1-(2,2-difluoroethyl)-3-({2-  
 [({5-[(4-ethylbenzoyl)amino]-1,3,4-thiadiazol-2-  
 yl)sulfonyl]amino)-2-oxoethyl}amino)-2,3-dioxopropyl]-1-  
 ((2*S*,3*R*)-3-methyl-2-[(9-oxo-9*H*-fluoren-1-  
 yl)carbonyl]amino}pentanoyl)-2-pyrrolidinecarboxamide;  
 10 *tert*-butyl {[ (3*S*)-3-({[(2*S*,4*R*)-4-(benzyloxy)-1-((2*S*,3*R*)-2-  
 {[5-(4-chlorophenyl)-2-furoyl]amino}-3-  
 methylpentanoyl)pyrrolidinyl]carbonyl}amino)-5,5-difluoro-  
 2-oxopentanoyl]amino}acetate;  
 15 {[ (3*S*)-3-({[(2*S*,4*R*)-4-(benzyloxy)-1-((2*S*,3*R*)-2-  
 {[5-(4-chlorophenyl)-2-furoyl]amino}-3-  
 methylpentanoyl)pyrrolidinyl]carbonyl}amino)-5,5-difluoro-  
 2-oxopentanoyl]amino}acetic acid;  
 20 (2*S*,4*R*)-*N*-[(1*S*)-3-{{2-({[5-(acetylamino)-1,3,4-thiadiazol-  
 2-yl)sulfonyl]amino)-2-oxoethyl}amino)-1-(2,2-  
 difluoroethyl)-2,3-dioxopropyl]-4-(benzyloxy)-1-((2*S*,3*R*)-2-  
 {[5-(4-chlorophenyl)-2-furoyl]amino}-3-methylpentanoyl)-2-  
 25 pyrrolidinecarboxamide;  
 (2*S*,4*R*)-4-(benzyloxy)-*N*-[(1*S*)-3-({2-[(5-[(3-  
 chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl]amino)-2-oxoethyl}amino)-1-(2,2-difluoroethyl)-2,3-dioxopropyl]-1-  
 30 ((2*S*,3*R*)-2-[[5-(4-chlorophenyl)-2-furoyl]amino]-3-  
 methylpentanoyl)-2-pyrrolidinecarboxamide;  
 (2*S*,4*R*)-4-(benzyloxy)-*N*-[(1*S*)-3-({2-[[1,1'-biphenyl]-3-  
 ylsulfonyl]amino)-2-oxoethyl}amino)-1-(2,2-difluoroethyl)-  
 35 2,3-dioxopropyl]-1-((2*S*,3*R*)-2-[[5-(4-chlorophenyl)-2-  
 furoyl]amino]-3-methylpentanoyl)-2-pyrrolidinecarboxamide;  
*N*-{(1*S*,4*S*,7*S*)-10-allyl-7-(cyclohexylmethyl)-1-isobutyl-4-  
 [(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-  
 40 tetraazahexadec-15-en-1-yl}-2-pyrazinecarboxamide;

- 5 (6*S*,9*S*,12*S*)-*N*,3-diallyl-6-(cyclohexylmethyl)-12-isobutyl-9-  
[(1*R*)-1-methylpropyl]-2,5,8,11,14-pentaoxo-16,16-diphenyl-  
4,7,10,13-tetraazahexadecan-1-amide;
- (4*S*,7*S*,10*S*)-*N*,13-diallyl-10-(cyclohexylmethyl)-4-isobutyl-  
10 7-[(1*R*)-1-methylpropyl]-2,5,8,11,14-pentaoxo-3,6,9,12-  
tetraazapentadecan-15-amide;
- N*-{(1*S*,4*S*,7*S*)-10-allyl-7-(cyclohexylmethyl)-1-isobutyl-4-  
[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-  
15 tetraazahexadec-15-en-1-yl}-2-pyridinecarboxamide;
- N*-{(1*S*,4*S*,7*S*)-10-allyl-7-(cyclohexylmethyl)-1-isobutyl-4-  
[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-  
20 tetraazahexadec-15-en-1-yl}nicotinamide;
- N*-{(1*S*,4*S*,7*S*)-10-allyl-7-(cyclohexylmethyl)-1-isobutyl-4-  
[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-  
25 tetraazahexadec-15-en-1-yl}-4-nitro-1*H*-pyrazole-3-  
carboxamide;
- 2-{(3*S*,6*S*,9*S*)-12-allyl-9-(cyclohexylmethyl)-3-isobutyl-6-  
[(1*R*)-1-methylpropyl]-4,7,10,13,14-pentaoxo-2,5,8,11,15-  
pentaazaoctadec-17-en-1-anoyl}benzoic acid;
- 30 *N*-[4-*sec*-butyl-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-  
2,5,8,11,12-pentaoxo-3,6,9,13-tetraazahexadec-15-en-1-  
yl]nicotinamide;
- N*-allyl-9-*sec*-butyl-6-(cyclohexylmethyl)-3-ethyl-12-  
35 isobutyl-2,5,8,11,14-pentaoxo-16,16-diphenyl-4,7,10,13-  
tetraazahexadecan-1-amide;
- {3-[(1-[(3-methyl-2-({4-methyl-2-[(2-  
pyrazinylcarbonyl)amino]pentanoyl}amino)pentanoyl]-  
40 octahydro-1*H*-indol-2-yl}carbonyl)amino]-2-  
oxopentanoyl}amino)acetic acid;





5 R<sup>10b</sup> is selected from the group: -CO<sub>2</sub>H, -NH<sub>2</sub>, -OH, -SH, and  
-C(=NH)NH<sub>2</sub>;

R<sup>10c</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

10 alternatively, R<sup>10</sup> and R<sup>10c</sup> can be combined to form a C<sub>3</sub>-C<sub>6</sub>  
cycloalkyl group substituted with 0-1 R<sup>10a</sup>;

R<sup>11</sup> is, at each occurrence, independently H or C<sub>1</sub>-C<sub>4</sub> alkyl;

15 R<sup>11a</sup> is H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl,  
C<sub>2</sub>-C<sub>4</sub> alkynyl, aryl, aryl(C<sub>1</sub>-C<sub>4</sub> alkyl)-,  
C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or C<sub>3</sub>-C<sub>6</sub> cycloalkyl(C<sub>1</sub>-C<sub>4</sub> alkyl)-;

Q<sup>1</sup> is selected from:

20 -CO<sub>2</sub>R<sup>11</sup>, -SO<sub>2</sub>R<sup>11</sup>, -SO<sub>3</sub>R<sup>11</sup>, -P(O)<sub>2</sub>R<sup>11</sup>, -P(O)<sub>3</sub>R<sup>11</sup>,  
aryl substituted with 0-4 Q<sup>1a</sup>, and  
5-6 membered heterocyclic group consisting of carbon  
atoms and 1-4 heteroatoms selected from the group:  
O, S, and N, said heterocyclic group substituted  
25 with 0-4 Q<sup>1a</sup>;

Q<sup>1a</sup> is H, F, Cl, Br, I, -NO<sub>2</sub>, -CN, -NCS, -CF<sub>3</sub>, -OCF<sub>3</sub>, -CH<sub>3</sub>,  
-OCH<sub>3</sub>, -CO<sub>2</sub>R<sup>19</sup>, -C(=O)NR<sup>19</sup>R<sup>19</sup>, -NHC(=O)R<sup>19</sup>, -SO<sub>2</sub>R<sup>19</sup>,  
-SO<sub>2</sub>NR<sup>19</sup>R<sup>19</sup>, -NR<sup>19</sup>R<sup>19</sup>, -OR<sup>19</sup>, -SR<sup>19</sup>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub>  
30 alkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkyl, or C<sub>1</sub>-C<sub>4</sub> haloalkoxy;

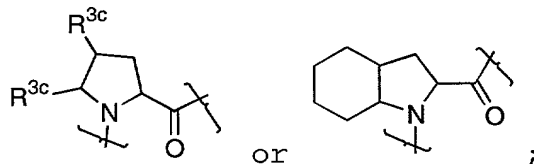
R<sup>19</sup> is C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, aryl, aryl(C<sub>1</sub>-C<sub>4</sub>  
alkyl), C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or C<sub>3</sub>-C<sub>6</sub> cycloalkyl(C<sub>1</sub>-C<sub>4</sub>  
alkyl);

35

alternatively, NR<sup>19</sup>R<sup>19</sup> may form a 5-6 membered heterocyclic  
group consisting of carbon atoms, a nitrogen atom, and  
optionally a second heteroatom selected from the  
group: O, S, and N;

5

A<sup>2</sup> is a bond, -NH-CR<sup>3</sup>R<sup>4</sup>-C(=O)-, an amino acid residue,



10

A<sup>3</sup> is a bond, -NH-CR<sup>5</sup>R<sup>6</sup>-C(=O)-, or an amino acid residue;

A<sup>4</sup> is a bond, -NH-CR<sup>7</sup>R<sup>8</sup>-C(=O)-, or an amino acid residue;

A<sup>5</sup> is a bond or an amino acid residue;

15 A<sup>7</sup> is a bond or an amino acid residue;

A<sup>8</sup> is an amino acid residue;

A<sup>9</sup> is an amino acid residue;

20

R<sup>1</sup> is selected from the group: H, F,

C<sub>1</sub>-C<sub>6</sub> alkyl substituted with 0-3 R<sup>1a</sup>,

C<sub>2</sub>-C<sub>6</sub> alkenyl substituted with 0-3 R<sup>1a</sup>,

C<sub>2</sub>-C<sub>6</sub> alkynyl substituted with 0-3 R<sup>1a</sup>, and

25 C<sub>3</sub>-C<sub>6</sub> cycloalkyl substituted with 0-3 R<sup>1a</sup>;

R<sup>1a</sup> is selected at each occurrence from the group:

Cl, F, Br, I, CF<sub>3</sub>, CHF<sub>2</sub>, OH, =O, SH,

-CO<sub>2</sub>R<sup>1b</sup>, -SO<sub>2</sub>R<sup>1b</sup>, -SO<sub>3</sub>R<sup>1b</sup>, -P(O)<sub>2</sub>R<sup>1b</sup>, -P(O)<sub>3</sub>R<sup>1b</sup>,

30 -C(=O)NHR<sup>1b</sup>, -NHC(=O)R<sup>1b</sup>, -SO<sub>2</sub>NHR<sup>1b</sup>, -OR<sup>1b</sup>, -SR<sup>1b</sup>,

C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy,

-S-(C<sub>1</sub>-C<sub>6</sub> alkyl),

aryl substituted with 0-5 R<sup>1c</sup>,

-O-(CH<sub>2</sub>)<sub>q</sub>-aryl substituted with 0-5 R<sup>1c</sup>,

35 -S-(CH<sub>2</sub>)<sub>q</sub>-aryl substituted with 0-5 R<sup>1c</sup>, and

5           5-10 membered heterocyclic group consisting of carbon  
          atoms and 1-4 heteroatoms selected from the group:  
          O, S, and N, and substituted with 0-3 R<sup>1c</sup>;

R<sup>1b</sup> is H,

10           C<sub>1</sub>-C<sub>4</sub> alkyl substituted with 0-3 R<sup>1c</sup>,  
          C<sub>2</sub>-C<sub>4</sub> alkenyl substituted with 0-3 R<sup>1c</sup>,  
          C<sub>2</sub>-C<sub>4</sub> alkynyl substituted with 0-3 R<sup>1c</sup>,  
          C<sub>3</sub>-C<sub>6</sub> cycloalkyl substituted with 0-5 R<sup>1c</sup>,  
          C<sub>3</sub>-C<sub>6</sub> carbocycle substituted with 0-5 R<sup>1c</sup>,  
15           aryl substituted with 0-5 R<sup>1c</sup>, or  
          5-6 membered heterocyclic group consisting of carbon  
          atoms and 1-4 heteroatoms selected from the group:  
          O, S, and N, said heterocyclic group substituted  
          with 0-4 R<sup>1c</sup>;

20           R<sup>1c</sup> is selected at each occurrence from: C<sub>1</sub>-C<sub>4</sub> alkyl, Cl,  
          F, Br, I, OH, C<sub>1</sub>-C<sub>4</sub> alkoxy, -CN, -NO<sub>2</sub>, C(O)OR<sup>1d</sup>,  
          NR<sup>1d</sup>R<sup>1d</sup>, CF<sub>3</sub>, and OCF<sub>3</sub>;

25           R<sup>1d</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sup>2</sup> is H, F, or C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sup>3</sup> is selected from the group: H,

30           C<sub>1</sub>-C<sub>6</sub> alkyl substituted with 0-4 R<sup>3a</sup>,  
          C<sub>2</sub>-C<sub>6</sub> alkenyl substituted with 0-4 R<sup>3a</sup>,  
          C<sub>2</sub>-C<sub>6</sub> alkynyl substituted with 0-4 R<sup>3a</sup>,  
          -(CH<sub>2</sub>)<sub>q</sub>- C<sub>3</sub>-C<sub>6</sub> cycloalkyl substituted with 0-4 R<sup>3b</sup>,  
          -(CH<sub>2</sub>)<sub>q</sub>-aryl substituted with 0-5 R<sup>3b</sup>, and  
35           -(CH<sub>2</sub>)<sub>q</sub>-5-10 membered heterocyclic group consisting of  
          carbon atoms and 1-4 heteroatoms selected from  
          the group: O, S, and N, and said heterocyclic  
          group is substituted with 0-2 R<sup>3b</sup>;

- 5  $R^{3a}$  is selected from the group:  $-CO_2R^{11}$ ,  $-NR^{11}R^{11}$ ,  $-OR^{11}$ ,  
 $-SR^{11}$ ,  $-C(=NH)NH_2$ , and aryl substituted with  $R^{10b}$ ;
- $R^{3b}$  is selected from the group:  $-CO_2H$ ,  $-NH_2$ ,  $-OH$ ,  $-SH$ , and  
 $-C(=NH)NH_2$ ;
- 10  $R^{3c}$  is, at each occurrence, independently selected from: H,  
 $C_1-C_6$  alkyl,  $-OH$ , and  $OR^{3d}$ ;
- $R^{3d}$  is  $C_1-C_6$  alkyl,  $C_2-C_6$  alkenyl,  $C_2-C_6$  alkynyl,  
15  $-(CH_2)_q-C_3-C_6$  cycloalkyl,  $-(CH_2)_q$ -aryl, or  
 $-(CH_2)_q$ -(5-10 membered heterocyclic group), wherein  
said heterocyclic group consists of carbon atoms  
and 1-4 heteroatoms selected from the group: O,  
S, and N;
- 20  $R^4$  is selected from the group: H,  $C_1-C_6$  alkyl, phenyl,  
phenylmethyl-, phenylethyl-,  $C_3-C_6$  cycloalkyl,  
 $C_3-C_6$  cycloalkylmethyl-, and  $C_3-C_6$  cycloalkylethyl-;
- 25  $R^5$  and  $R^7$  are independently H or  $R^3$ ;
- $R^6$  and  $R^8$  are independently H or  $R^4$ ;
- $R^9$  is selected from the group:  $-S(=O)R^{9a}$ ,  $-S(=O)_2R^{9a}$ ,  
30  $-C(=O)R^{9a}$ ,  $-C(=O)OR^{9a}$ ,  $-C(=O)NHR^{9a}$ ,  $C_1-C_3$  alkyl- $R^{9a}$ ,  
 $C_2-C_6$  alkenyl- $R^{9a}$ , and  $C_2-C_6$  alkynyl- $R^{9a}$ ;
- $R^{9a}$  is selected from the group:  
 $C_1-C_6$  alkyl substituted with 0-3  $R^{9b}$ ,  
35  $C_3-C_6$  cycloalkyl substituted with 0-3  $R^{9c}$ ,  
aryl substituted with 0-3  $R^{9c}$ , and  
5-14 membered heterocyclic group consisting of carbon  
atoms and 1-4 heteroatoms selected from the

5 group: O, S, and N, and said heterocyclic group  
is substituted with 0-3 R<sup>9c</sup>;

R<sup>9b</sup> is selected from the group: phenyl, naphthyl, benzyl,  
and 5-10 membered heterocyclic group consisting of  
10 carbon atoms and 1-4 heteroatoms selected from the  
group: O, S, and N, and R<sup>9b</sup> is substituted with 0-3  
R<sup>9c</sup>;

R<sup>9c</sup> is selected at each occurrence from the group:

15 CF<sub>3</sub>, OCF<sub>3</sub>, Cl, F, Br, I, =O, OH, phenyl, C(O)OR<sup>11</sup>, NH<sub>2</sub>,  
NH(CH<sub>3</sub>), N(CH<sub>3</sub>)<sub>2</sub>, -CN, NO<sub>2</sub>;  
C<sub>1</sub>-C<sub>4</sub> alkyl substituted with 0-3 R<sup>9d</sup>,  
C<sub>1</sub>-C<sub>4</sub> alkoxy substituted with 0-3 R<sup>9d</sup>,  
C<sub>3</sub>-C<sub>6</sub> cycloalkyl substituted with 0-3 R<sup>9d</sup>,  
20 aryl substituted with 0-5 R<sup>9d</sup>, and  
5-6 membered heterocyclic group consisting of carbon  
atoms and 1-4 heteroatoms selected from the  
group: O, S, and N, and said heterocyclic group  
is substituted with 0-4 R<sup>9d</sup>;

25 R<sup>9d</sup> is selected at each occurrence from the group:  
C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CF<sub>3</sub>, OCF<sub>3</sub>, Cl, F, Br, I, =O,  
OH, phenyl, C(O)OR<sup>11</sup>, NH<sub>2</sub>, NH(CH<sub>3</sub>), N(CH<sub>3</sub>)<sub>2</sub>, -CN,  
and NO<sub>2</sub>;

30 n is 1, 2, or 3; and

p is 1 or 2; and

35 q, at each occurrence, is independently 0, 1 or 2.

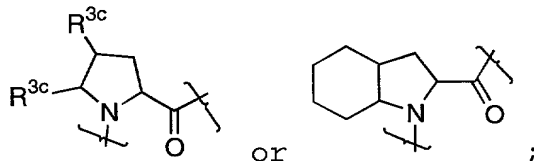
[10] In a further more preferred embodiment, the present  
invention provides novel compounds of Formula IIb, wherein:

- 5  $R^{10}$  is selected from the group:  $-CO_2R^{11}$ ,  $-NR^{11}R^{11}$ , and  $C_1-C_6$  alkyl substituted with 0-1  $R^{10a}$ ;
- $R^{10a}$  is selected from the group: halo,  $-NO_2$ ,  $-CN$ ,  $-CF_3$ ,  $-CO_2R^{11}$ ,  $-NR^{11}R^{11}$ ,  $-OR^{11}$ ,  $-SR^{11}$ ,  $-C(=NH)NH_2$ , and aryl substituted with 0-1  $R^{10b}$ ;
- 10  $R^{10b}$  is selected from the group:  $-CO_2H$ ,  $-NH_2$ ,  $-OH$ ,  $-SH$ , and  $-C(=NH)NH_2$ ;
- 15  $R^{10c}$  is H or  $C_1-C_4$  alkyl;
- alternatively,  $R^{10}$  and  $R^{10c}$  can be combined to form a  $C_3-C_6$  cycloalkyl group substituted with 0-1  $R^{10a}$ ;
- 20  $R^{11}$  is, at each occurrence, independently H or  $C_1-C_4$  alkyl;
- $R^{11a}$  is H,  $C_1-C_4$  alkyl,  $C_1-C_4$  haloalkyl,  $C_2-C_4$  alkenyl,  $C_2-C_4$  alkynyl, aryl, aryl( $C_1-C_4$  alkyl)-,  $C_3-C_6$  cycloalkyl, or  $C_3-C_6$  cycloalkyl( $C_1-C_4$  alkyl)-;
- 25  $Q^1$  is selected from:
- $-CO_2R^{11}$ ,  $-SO_2R^{11}$ ,  $-SO_3R^{11}$ ,  $-P(O)_2R^{11}$ ,  $-P(O)_3R^{11}$ , aryl substituted with 0-4  $Q^{1a}$ , and 5-6 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group:
- 30 O, S, and N, said heterocyclic group substituted with 0-4  $Q^{1a}$ ;
- $Q^{1a}$  is H, F, Cl, Br, I,  $-NO_2$ ,  $-CN$ ,  $-NCS$ ,  $-CF_3$ ,  $-OCF_3$ ,  $-CH_3$ ,  $-OCH_3$ ,  $-CO_2R^{19}$ ,  $-C(=O)NR^{19}R^{19}$ ,  $-NHC(=O)R^{19}$ ,  $-SO_2R^{19}$ ,  $-SO_2NR^{19}R^{19}$ ,  $-NR^{19}R^{19}$ ,  $-OR^{19}$ ,  $-SR^{19}$ ,  $C_1-C_4$  alkyl,  $C_1-C_4$  alkoxy,  $C_1-C_4$  haloalkyl, or  $C_1-C_4$  haloalkoxy;
- 35

5  $R^{19}$  is  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  haloalkyl, aryl, aryl( $C_1$ - $C_4$  alkyl),  $C_3$ - $C_6$  cycloalkyl, or  $C_3$ - $C_6$  cycloalkyl( $C_1$ - $C_4$  alkyl);

alternatively,  $NR^{19}R^{19}$  may form a piperidinyl, piperazinyl,  
10 or morpholinyl group;

$A^2$  is a bond,  $-NH-CR^3R^4-C(=O)-$ , an amino acid residue,



15  $A^3$  is a bond or an amino acid residue;

$A^4$  is a bond or an amino acid residue;

$A^5$  is a bond;

20

$R^1$  is selected from the group: H,

$C_1$ - $C_6$  alkyl substituted with 0-3  $R^{1a}$ ,

$C_2$ - $C_6$  alkenyl substituted with 0-3  $R^{1a}$ ,

$C_2$ - $C_6$  alkynyl substituted with 0-3  $R^{1a}$ , and

25  $C_3$ - $C_6$  cycloalkyl substituted with 0-3  $R^{1a}$ ;

$R^{1a}$  is selected at each occurrence from the group:

Cl, F, Br, I,  $CF_3$ ,  $CHF_2$ , OH, =O, SH,

$-CO_2R^{1b}$ ,  $-SO_2R^{1b}$ ,  $-SO_3R^{1b}$ ,  $-P(O)_2R^{1b}$ ,  $-P(O)_3R^{1b}$ ,

30  $-C(=O)NHR^{1b}$ ,  $-NHC(=O)R^{1b}$ ,  $-SO_2NHR^{1b}$ ,  $-OR^{1b}$ ,  $-SR^{1b}$ ,

$C_1$ - $C_3$  alkyl,  $C_3$ - $C_6$  cycloalkyl,  $C_1$ - $C_6$  alkoxy,

$-S-(C_1-C_6 \text{ alkyl})$ ,

aryl substituted with 0-5  $R^{1c}$ ,

$-O-(CH_2)_q$ -aryl substituted with 0-5  $R^{1c}$ ,

35  $-S-(CH_2)_q$ -aryl substituted with 0-5  $R^{1c}$ , and

5           5-10 membered heterocyclic group consisting of carbon  
          atoms and 1-4 heteroatoms selected from the group:  
          O, S, and N, and substituted with 0-3 R<sup>1c</sup>;

R<sup>1b</sup> is H,

10           C<sub>1</sub>-C<sub>4</sub> alkyl substituted with 0-3 R<sup>1c</sup>,  
          C<sub>2</sub>-C<sub>4</sub> alkenyl substituted with 0-3 R<sup>1c</sup>,  
          C<sub>2</sub>-C<sub>4</sub> alkynyl substituted with 0-3 R<sup>1c</sup>,  
          C<sub>3</sub>-C<sub>6</sub> cycloalkyl substituted with 0-5 R<sup>1c</sup>,  
          C<sub>3</sub>-C<sub>6</sub> carbocycle substituted with 0-5 R<sup>1c</sup>,  
15           aryl substituted with 0-5 R<sup>1c</sup>, or  
          5-6 membered heterocyclic group consisting of carbon  
          atoms and 1-4 heteroatoms selected from the group:  
          O, S, and N, said heterocyclic group substituted  
          with 0-4 R<sup>1c</sup>;

20           R<sup>1c</sup> is selected at each occurrence from: C<sub>1</sub>-C<sub>4</sub> alkyl, Cl,  
          F, Br, I, OH, C<sub>1</sub>-C<sub>4</sub> alkoxy, -CN, -NO<sub>2</sub>, C(O)OR<sup>1d</sup>,  
          NR<sup>1d</sup>R<sup>1d</sup>, CF<sub>3</sub>, and OCF<sub>3</sub>;

25           R<sup>1d</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sup>2</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sup>3</sup> is selected from the group: H,

30           C<sub>1</sub>-C<sub>6</sub> alkyl substituted with 0-4 R<sup>3a</sup>,  
          C<sub>2</sub>-C<sub>6</sub> alkenyl substituted with 0-4 R<sup>3a</sup>,  
          C<sub>2</sub>-C<sub>6</sub> alkynyl substituted with 0-4 R<sup>3a</sup>,  
          -(CH<sub>2</sub>)<sub>q</sub>- C<sub>3</sub>-C<sub>6</sub> cycloalkyl substituted with 0-4 R<sup>3b</sup>,  
          -(CH<sub>2</sub>)<sub>q</sub>-aryl substituted with 0-5 R<sup>3b</sup>, and  
35           -(CH<sub>2</sub>)<sub>q</sub>-5-10 membered heterocyclic group consisting of  
          carbon atoms and 1-4 heteroatoms selected from  
          the group: O, S, and N, and said heterocyclic  
          group is substituted with 0-2 R<sup>3b</sup>;



5 R<sup>3a</sup> is selected from the group: -CO<sub>2</sub>R<sup>11</sup>, -NR<sup>11</sup>R<sup>11</sup>, -OR<sup>11</sup>,  
-SR<sup>11</sup>, -C(=NH)NH<sub>2</sub>, and aryl substituted with R<sup>10b</sup>;

R<sup>3b</sup> is selected from the group: -CO<sub>2</sub>H, - NH<sub>2</sub>, -OH, -SH, and  
-C(=NH)NH<sub>2</sub>;

10

R<sup>3c</sup> is, at each occurrence, independently selected from: H,  
C<sub>1</sub>-C<sub>6</sub> alkyl, -OH, and OR<sup>3d</sup>;

R<sup>3d</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl,  
15 -(CH<sub>2</sub>)<sub>q</sub>- C<sub>3</sub>-C<sub>6</sub> cycloalkyl, -(CH<sub>2</sub>)<sub>q</sub>-aryl, or  
-(CH<sub>2</sub>)<sub>q</sub>-(5-10 membered heterocyclic group), wherein  
said heterocyclic group consists of carbon atoms  
and 1-4 heteroatoms selected from the group: O,  
S, and N;

20

R<sup>4</sup> is selected from the group: H, C<sub>1</sub>-C<sub>6</sub> alkyl, phenyl,  
phenylmethyl-, phenylethyl-, C<sub>3</sub>-C<sub>6</sub> cycloalkyl,  
C<sub>3</sub>-C<sub>6</sub> cycloalkylmethyl-, and C<sub>3</sub>-C<sub>6</sub> cycloalkylethyl-;

25 R<sup>9</sup> is selected from the group: -S(=O)<sub>2</sub>R<sup>9a</sup>, -C(=O)R<sup>9a</sup>,  
C<sub>1</sub>-C<sub>3</sub> alkyl-R<sup>9a</sup>, C<sub>2</sub>-C<sub>6</sub> alkenyl-R<sup>9a</sup>, and  
C<sub>2</sub>-C<sub>6</sub> alkynyl-R<sup>9a</sup>;

R<sup>9a</sup> is selected from the group:

30 C<sub>1</sub>-C<sub>6</sub> alkyl substituted with 0-3 R<sup>9b</sup>,  
C<sub>3</sub>-C<sub>6</sub> cycloalkyl substituted with 0-3 R<sup>9c</sup>,  
aryl substituted with 0-3 R<sup>9c</sup>, and  
5-14 membered heterocyclic group consisting of carbon  
atoms and 1-4 heteroatoms selected from the  
35 group: O, S, and N, and said heterocyclic group  
is substituted with 0-3 R<sup>9c</sup>;

R<sup>9b</sup> is selected from the group: phenyl, naphthyl, benzyl,  
and 5-10 membered heterocyclic group consisting of

5 carbon atoms and 1-4 heteroatoms selected from the  
group: O, S, and N, and R<sup>9b</sup> is substituted with 0-3  
R<sup>9c</sup>;

R<sup>9c</sup> is selected at each occurrence from the group:

10 CF<sub>3</sub>, OCF<sub>3</sub>, Cl, F, Br, I, =O, OH, phenyl, C(O)OR<sup>11</sup>, NH<sub>2</sub>,  
NH(CH<sub>3</sub>), N(CH<sub>3</sub>)<sub>2</sub>, -CN, NO<sub>2</sub>;  
C<sub>1</sub>-C<sub>4</sub> alkyl substituted with 0-3 R<sup>9d</sup>,  
C<sub>1</sub>-C<sub>4</sub> alkoxy substituted with 0-3 R<sup>9d</sup>,  
C<sub>3</sub>-C<sub>6</sub> cycloalkyl substituted with 0-3 R<sup>9d</sup>,  
15 aryl substituted with 0-5 R<sup>9d</sup>, and  
5-6 membered heterocyclic group consisting of carbon  
atoms and 1-4 heteroatoms selected from the  
group: O, S, and N, and said heterocyclic group  
is substituted with 0-4 R<sup>9d</sup>;

20 R<sup>9d</sup> is selected at each occurrence from the group:

C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CF<sub>3</sub>, OCF<sub>3</sub>, Cl, F, Br, I, =O,  
OH, phenyl, C(O)OR<sup>11</sup>, NH<sub>2</sub>, NH(CH<sub>3</sub>), N(CH<sub>3</sub>)<sub>2</sub>, -CN, and  
NO<sub>2</sub>;

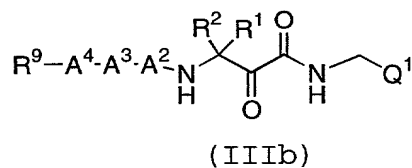
25 n is 1 or 2; and

p is 1 or 2; and

30 q, at each occurrence, is independently 0, 1 or 2.

[11] In an even more preferred embodiment, the present  
invention provides novel compounds of Formula IIIb,  
wherein:

35



5 or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

$Q^1$  is selected from:

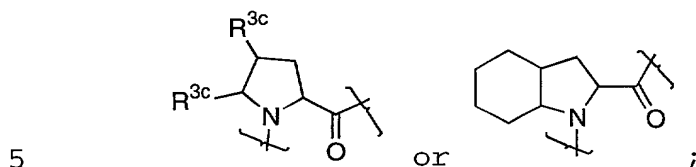
-CO<sub>2</sub>R<sup>11</sup>, -SO<sub>2</sub>R<sup>11</sup>, -SO<sub>3</sub>R<sup>11</sup>, -P(O)<sub>2</sub>R<sup>11</sup>, -P(O)<sub>3</sub>R<sup>11</sup>,  
10 aryl substituted with 0-4  $Q^{1a}$ , and  
5-6 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl,  
15 imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxazolidinyl, tetrahydrofuranlyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, and triazolyl; said heterocyclic group substituted with 0-4  $Q^{1a}$ ;

20  $Q^{1a}$  is H, F, Cl, Br, I, -NO<sub>2</sub>, -CN, -NCS, -CF<sub>3</sub>, -OCF<sub>3</sub>, -CH<sub>3</sub>, -OCH<sub>3</sub>, -CO<sub>2</sub>R<sup>19</sup>, -C(=O)NR<sup>19</sup>R<sup>19</sup>, -NHC(=O)R<sup>19</sup>, -SO<sub>2</sub>R<sup>19</sup>, -SO<sub>2</sub>NR<sup>19</sup>R<sup>19</sup>, -NR<sup>19</sup>R<sup>19</sup>, -OR<sup>19</sup>, -SR<sup>19</sup>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkyl, or C<sub>1</sub>-C<sub>4</sub> haloalkoxy;

25 R<sup>19</sup> is C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, aryl, aryl(C<sub>1</sub>-C<sub>4</sub> alkyl), C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or C<sub>3</sub>-C<sub>6</sub> cycloalkyl(C<sub>1</sub>-C<sub>4</sub> alkyl);

30 alternatively, NR<sup>19</sup>R<sup>19</sup> may form a piperidinyl, piperazinyl, or morpholinyl group;

A<sup>2</sup> is a bond, -NH-CR<sup>3</sup>R<sup>4</sup>-C(=O)-, Ala, Arg, Asn, Asp, Aze, Cha, Cys, Dpa, Gln, Glu, Gly, His, Hyp, Ile, Irg, Leu,  
35 Lys, Met, Orn, Phe, Phe(4-fluoro), Pro, Sar, Ser, Thr, Trp, Tyr, Val,



$A^3$  is a bond, Ala, Arg, Asn, Asp, Aze, Cha, Cys, Dpa, Gln, Glu, Gly, His, Hyp, Ile, Irg, Leu, Lys, Met, Orn, Phe, Phe(4-fluoro), Pro, Sar, Ser, Thr, Trp, Tyr, or Val;

10

$A^4$  is a bond, Ala, Arg, Asn, Asp, Aze, Cha, Cys, Dpa, Gln, Glu, Gly, His, Hyp, Ile, Irg, Leu, Lys, Met, Orn, Phe, Phe(4-fluoro), Pro, Sar, Ser, Thr, Trp, Tyr, or Val;

15  $R^1$  is selected from the group: H,

$C_1$ - $C_6$  alkyl substituted with 0-3  $R^{1a}$ ,

$C_2$ - $C_6$  alkenyl substituted with 0-3  $R^{1a}$ ,

$C_2$ - $C_6$  alkynyl substituted with 0-3  $R^{1a}$ , and

$C_3$ - $C_6$  cycloalkyl substituted with 0-3  $R^{1a}$ ;

20

$R^{1a}$  is selected at each occurrence from the group:

Cl, F, Br, I,  $CF_3$ ,  $CHF_2$ , OH, =O, SH,

$-CO_2R^{1b}$ ,  $-SO_2R^{1b}$ ,  $-SO_3R^{1b}$ ,  $-P(O)_2R^{1b}$ ,  $-P(O)_3R^{1b}$ ,

$-C(=O)NHR^{1b}$ ,  $-NHC(=O)R^{1b}$ ,  $-SO_2NHR^{1b}$ ,  $-OR^{1b}$ ,  $-SR^{1b}$ ,

25

$C_1$ - $C_3$  alkyl,  $C_3$ - $C_6$  cycloalkyl,  $C_1$ - $C_6$  alkoxy,

$-S-(C_1-C_6 \text{ alkyl})$ ,

aryl substituted with 0-5  $R^{1c}$ ,

$-O-(CH_2)_q$ -aryl substituted with 0-5  $R^{1c}$ ,

$-S-(CH_2)_q$ -aryl substituted with 0-5  $R^{1c}$ , and

30

5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group:

pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl,

pyrazinyl, piperazinyl, piperidinyl, imidazolyl,

imidazolidinyl, indolyl, tetrazolyl, isoxazolyl,

35

morpholinyl, oxazolyl, oxazolidinyl,

tetrahydrofuranyl, thiadiazinyl, thiadiazolyl,

thiazolyl, triazinyl, triazolyl, benzimidazolyl,

5 1*H*-indazolyl, benzofuranyl, benzothiofuranyl,  
benztetrazolyl, benzotriazolyl, benzisoxazolyl,  
benzoxazolyl, oxindolyl, benzoxazoliny,   
benzthiazolyl, benzisothiazolyl, isatinoyl,  
isoquinoliny, octahydroisoquinoliny,   
10 tetrahydroisoquinoliny, tetrahydroquinoliny,   
isoxazolopyridiny, quinazoliny, quinoliny,   
isothiazolopyridiny, thiazolopyridiny,   
oxazolopyridiny, imidazolopyridiny, and   
pyrazolopyridiny; and substituted with 0-3 R<sup>1c</sup>;

15

R<sup>1b</sup> is H,

C<sub>1</sub>-C<sub>4</sub> alkyl substituted with 0-3 R<sup>1c</sup>,  
C<sub>2</sub>-C<sub>4</sub> alkenyl substituted with 0-3 R<sup>1c</sup>,  
C<sub>2</sub>-C<sub>4</sub> alkynyl substituted with 0-3 R<sup>1c</sup>,  
20 C<sub>3</sub>-C<sub>6</sub> cycloalkyl substituted with 0-5 R<sup>1c</sup>,  
C<sub>3</sub>-C<sub>6</sub> carbocycle substituted with 0-5 R<sup>1c</sup>,  
aryl substituted with 0-5 R<sup>1c</sup>, or  
5-6 membered heterocyclic group consisting of carbon  
atoms and 1-4 heteroatoms selected from the group:  
25 pyridiny, furanyl, thienyl, pyrrolyl, pyrazolyl,  
pyraziny, piperaziny, piperidiny, imidazolyl,  
imidazolidiny, indolyl, tetrazolyl, isoxazolyl,  
morpholiny, oxazolyl, oxazolidiny,   
tetrahydrofuranyl, thiadiaziny, thiadiazolyl,  
30 thiazolyl, triaziny, and triazolyl; said  
heterocyclic group substituted with 0-4 R<sup>1c</sup>;

R<sup>1c</sup> is selected at each occurrence from: C<sub>1</sub>-C<sub>4</sub> alkyl, Cl,  
F, Br, I, OH, C<sub>1</sub>-C<sub>4</sub> alkoxy, -CN, -NO<sub>2</sub>, C(O)OR<sup>1d</sup>,  
35 NR<sup>1d</sup>R<sup>1d</sup>, CF<sub>3</sub>, and OCF<sub>3</sub>;

R<sup>1d</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sup>2</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

40

5     $R^3$  is selected from the group: H,  
        $C_1-C_6$  alkyl substituted with 0-4  $R^{3a}$ ,  
        $C_2-C_6$  alkenyl substituted with 0-4  $R^{3a}$ ,  
        $C_2-C_6$  alkynyl substituted with 0-4  $R^{3a}$ ,  
        $-(CH_2)_q-$   $C_3-C_6$  cycloalkyl substituted with 0-4  $R^{3b}$ ,  
 10     $-(CH_2)_q$ -aryl substituted with 0-5  $R^{3b}$ , and  
        $-(CH_2)_q$ -5-10 membered heterocyclic group consisting of  
       carbon atoms and 1-4 heteroatoms selected from  
       the group: pyridinyl, furanyl, thienyl, pyrrolyl,  
       pyrazolyl, pyrazinyl, piperazinyl, piperidinyl,  
 15    imidazolyl, imidazolidinyl, indolyl, tetrazolyl,  
       isoxazolyl, morpholinyl, oxazolyl, oxazolidinyl,  
       tetrahydrofuranyl, thiadiazinyl, thiadiazolyl,  
       thiazolyl, triazinyl, triazolyl, benzimidazolyl,  
       1*H*-indazolyl, benzofuranyl, benzothiofuranyl,  
 20    benztetrazolyl, benzotriazolyl, benzisoxazolyl,  
       benzoxazolyl, oxindolyl, benzoxazolinyl,  
       benzthiazolyl, benzisothiazolyl, isatinoyl,  
       isoquinolinyl, octahydroisoquinolinyl,  
       tetrahydroisoquinolinyl, tetrahydroquinolinyl,  
 25    isoxazolopyridinyl, quinazolinyl, quinolinyl,  
       isothiazolopyridinyl, thiazolopyridinyl,  
       oxazolopyridinyl, imidazolopyridinyl, and  
       pyrazolopyridinyl; and said heterocyclic group  
       is substituted with 0-2  $R^{3b}$ ;

30     $R^{3a}$  is selected from the group:  $-CO_2R^{11}$ ,  $-NR^{11}R^{11}$ ,  $-OR^{11}$ ,  
        $-SR^{11}$ ,  $-C(=NH)NH_2$ , and aryl substituted with  $R^{10b}$ ;

35     $R^{3b}$  is selected from the group:  $-CO_2H$ ,  $-NH_2$ ,  $-OH$ ,  $-SH$ , and  
        $-C(=NH)NH_2$ ;

$R^{3c}$  is, at each occurrence, independently selected from: H,  
        $C_1-C_6$  alkyl,  $-OH$ , and  $OR^{3d}$ ;

40     $R^{3d}$  is  $C_1-C_6$  alkyl,  $C_2-C_6$  alkenyl,  $C_2-C_6$  alkynyl,

- 5            $-(CH_2)_q$ - C<sub>3</sub>-C<sub>6</sub> cycloalkyl,  $-(CH_2)_q$ -aryl, or  
           $-(CH_2)_q$ -(5-10 membered heterocyclic group), wherein  
          said heterocyclic group consists of carbon atoms  
          and 1-4 heteroatoms selected from the group: O,  
          S, and N;
- 10           R<sup>4</sup> is selected from the group: H, C<sub>1</sub>-C<sub>6</sub> alkyl, phenyl,  
          phenylmethyl-, phenylethyl-, C<sub>3</sub>-C<sub>6</sub> cycloalkyl,  
          C<sub>3</sub>-C<sub>6</sub> cycloalkylmethyl-, and C<sub>3</sub>-C<sub>6</sub> cycloalkylethyl-;
- 15           R<sup>9</sup> is selected from  $-S(=O)_2R^{9a}$  and  $-C(=O)R^{9a}$ ;
- R<sup>9a</sup> is selected from the group:  
          phenyl substituted with 0-3 R<sup>9c</sup>,  
          naphthyl substituted with 0-3 R<sup>9c</sup>, and
- 20           5-14 membered heterocyclic group consisting of carbon  
          atoms and 1-4 heteroatoms selected from the  
          group: pyridinyl, furanyl, thienyl, pyrrolyl,  
          pyrazolyl, pyrazinyl, piperazinyl, piperidinyl,  
          imidazolyl, imidazolidinyl, indolyl, tetrazolyl,  
25           isoxazolyl, morpholinyl, oxazolyl, oxazolidinyl,  
          tetrahydrofuranyl, thiadiazinyl, thiadiazolyl,  
          thiazolyl, triazinyl, triazolyl, benzimidazolyl,  
          1*H*-indazolyl, benzofuranyl, benzothiofuranyl,  
          benztetrazolyl, benzotriazolyl, benzisoxazolyl,  
30           benzoxazolyl, oxindolyl, benzoxazolinyl,  
          benzthiazolyl, benzisothiazolyl, isatinoyl,  
          isoquinolinyl, octahydroisoquinolinyl,  
          tetrahydroisoquinolinyl, tetrahydroquinolinyl,  
          isoxazolopyridinyl, quinazolinyl, quinolinyl,  
35           isothiazolopyridinyl, thiazolopyridinyl,  
          oxazolopyridinyl, imidazolopyridinyl, and  
          pyrazolopyridinyl; and said heterocyclic group is  
          substituted with 0-3 R<sup>9c</sup>;
- 40           R<sup>9c</sup> is selected at each occurrence from the group:

5           CF<sub>3</sub>, OCF<sub>3</sub>, Cl, F, Br, I, =O, OH, phenyl, C(O)OR<sup>11</sup>, NH<sub>2</sub>,  
          NH(CH<sub>3</sub>), N(CH<sub>3</sub>)<sub>2</sub>, -CN, NO<sub>2</sub>;  
          C<sub>1</sub>-C<sub>4</sub> alkyl substituted with 0-3 R<sup>9d</sup>,  
          C<sub>1</sub>-C<sub>4</sub> alkoxy substituted with 0-3 R<sup>9d</sup>,  
          C<sub>3</sub>-C<sub>6</sub> cycloalkyl substituted with 0-3 R<sup>9d</sup>,  
10          aryl substituted with 0-5 R<sup>9d</sup>, and  
          5-6 membered heterocyclic group consisting of carbon  
          atoms and 1-4 heteroatoms selected from the  
          group: pyridinyl, furanyl, thienyl, pyrrolyl,  
          pyrazolyl, pyrazinyl, piperazinyl, piperidinyl,  
15          imidazolyl, imidazolidinyl, indolyl, tetrazolyl,  
          isoxazolyl, morpholinyl, oxazolyl, oxazolidinyl,  
          tetrahydrofuranyl, thiadiazinyl, thiadiazolyl,  
          thiazolyl, triazinyl, and triazolyl; and said  
          heterocyclic group is substituted with 0-4 R<sup>9d</sup>;  
20          R<sup>9d</sup> is selected at each occurrence from the group:  
          C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CF<sub>3</sub>, OCF<sub>3</sub>, Cl, F, Br, I, =O,  
          OH, phenyl, C(O)OR<sup>11</sup>, NH<sub>2</sub>, NH(CH<sub>3</sub>), N(CH<sub>3</sub>)<sub>2</sub>, -CN,  
          and NO<sub>2</sub>;  
25          p is 1 or 2; and  
  
          q, at each occurrence, is independently 0, 1 or 2.

30          In another embodiment, the present invention provides  
a novel pharmaceutical composition comprising a  
pharmaceutically acceptable carrier and a therapeutically  
effective amount of a compound of Formula (I), (II), (III),  
(IIb), (IIIb) or pharmaceutically acceptable salt form  
35 thereof.

          In another embodiment, the present invention provides  
a novel method of treating HCV infection which comprises  
administering to a host in need of such treatment a  
40 therapeutically effective amount of a compound of Formula



5 (I), (II), (III), (IIb), (IIIb) or pharmaceutically acceptable salt form thereof.

In another embodiment, the present invention provides novel compounds of Formula (I), (II), (III), (IIb), (IIIb) or pharmaceutically acceptable salt forms thereof for use in therapy.

In another embodiment, the present invention provides the use of novel compounds of Formula (I), (II), (III), (IIb), (IIIb) or pharmaceutically acceptable salt forms thereof for the manufacture of a medicament for the treatment of HCV.

#### DEFINITIONS

20 The compounds herein described have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Geometric isomers of double bonds such as olefins and C=N double bonds can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention.

30 Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated. All processes used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention.

40 The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that

5 the designated atom's normal valency is not exceeded, and  
that the substitution results in a stable compound. When a  
substituent is keto (i.e., =O), then 2 hydrogens on the  
atom are replaced. Keto substituents are not present on  
aromatic moieties. When a ring system (e.g., carbocyclic  
10 or heterocyclic) is said to be substituted with a carbonyl  
group or a double bond, it is intended that the carbonyl  
group or double bond be part (i.e., within) of the ring.

The present invention is intended to include all  
isotopes of atoms occurring in the present compounds.  
15 Isotopes include those atoms having the same atomic number  
but different mass numbers. By way of general example and  
without limitation, isotopes of hydrogen include tritium  
and deuterium. Isotopes of carbon include C-13 and C-14.

When any variable (e.g., R<sup>1a</sup>) occurs more than one  
20 time in any constituent or formula for a compound, its  
definition at each occurrence is independent of its  
definition at every other occurrence. Thus, for example,  
if a group is shown to be substituted with 0-3 R<sup>1a</sup>, then  
said group may optionally be substituted with up to three  
25 R<sup>1a</sup> groups and R<sup>1a</sup> at each occurrence is selected  
independently from the definition of R<sup>1a</sup>. Also,  
combinations of substituents and/or variables are  
permissible only if such combinations result in stable  
compounds.

30 When a bond to a substituent is shown to cross a bond  
connecting two atoms in a ring, then such substituent may  
be bonded to any atom on the ring. When a substituent is  
listed without indicating the atom via which such  
substituent is bonded to the rest of the compound of a  
35 given formula, then such substituent may be bonded via any  
atom in such substituent. Combinations of substituents  
and/or variables are permissible only if such combinations  
result in stable compounds.

As used herein, "alkyl" or "alkylene" is intended to  
40 include both branched and straight-chain saturated  
aliphatic hydrocarbon groups having the specified number of

5 carbon atoms. For example, "C<sub>1</sub>-C<sub>10</sub> alkyl" (or alkylene),  
is intended to include C<sub>1</sub>, C<sub>2</sub>, C<sub>3</sub>, C<sub>4</sub>, C<sub>5</sub>, C<sub>6</sub>, C<sub>7</sub>, C<sub>8</sub>, C<sub>9</sub>,  
and C<sub>10</sub> alkyl groups. Additionally, for example, "C<sub>1</sub>-C<sub>6</sub>  
alkyl" denotes alkyl having 1 to 6 carbon atoms. Examples  
of alkyl include, but are not limited to, methyl, ethyl,  
10 n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl,  
n-pentyl, n-hexyl, 2-methylbutyl, 2-methylpentyl, 2-  
ethylbutyl, 3-methylpentyl, and 4-methylpentyl.

"Alkenyl" or "alkenylene" is intended to include  
hydrocarbon chains of either a straight or branched  
15 configuration having the specified number of carbon atoms  
and one or more unsaturated carbon-carbon bonds which may  
occur in any stable point along the chain. For example,  
"C<sub>2</sub>-C<sub>6</sub> alkenyl" (or alkenylene), is intended to include C<sub>2</sub>,  
C<sub>3</sub>, C<sub>4</sub>, C<sub>5</sub>, and C<sub>6</sub> alkenyl groups. Examples of alkenyl  
20 include, but are not limited to, ethenyl, 1-propenyl, 2-  
propenyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-  
pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-  
methyl-2-propenyl, 4-methyl-3-pentenyl, and the like.

"Alkynyl" or "alkynylene" is intended to include  
hydrocarbon chains of either a straight or branched  
25 configuration and one or more carbon-carbon triple bonds  
which may occur in any stable point along the chain. For  
example, "C<sub>2</sub>-C<sub>6</sub> alkynyl" (or alkynylene), is intended to  
include C<sub>2</sub>, C<sub>3</sub>, C<sub>4</sub>, C<sub>5</sub>, and C<sub>6</sub> alkynyl groups; such as  
30 ethynyl, propynyl, butynyl, pentynyl, hexynyl and the like.

"Cycloalkyl" is intended to include saturated ring  
groups, having the specified number of carbon atoms. For  
example, "C<sub>3</sub>-C<sub>6</sub> cycloalkyl" denotes such as cyclopropyl,  
cyclobutyl, cyclopentyl, or cyclohexyl.

35 "Alkoxy" or "alkyloxy" represents an alkyl group as  
defined above with the indicated number of carbon atoms  
attached through an oxygen bridge. For example, "C<sub>1</sub>-C<sub>6</sub>  
alkoxy" (or alkyloxy), is intended to include C<sub>1</sub>, C<sub>2</sub>, C<sub>3</sub>,  
C<sub>4</sub>, C<sub>5</sub>, and C<sub>6</sub> alkoxy groups. Examples of alkoxy include,  
40 but are not limited to, methoxy, ethoxy, n-propoxy,  
i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy, and

5 s-pentoxy. Similarly, "alkylthio" or "thioalkoxy"  
represents an alkyl group as defined above with the  
indicated number of carbon atoms attached through a sulphur  
bridge.

"Halo" or "halogen" as used herein refers to fluoro,  
10 chloro, bromo, and iodo; and "counterion" is used to  
represent a small, negatively charged species such as  
chloride, bromide, hydroxide, acetate, sulfate, and the  
like.

"Haloalkyl" is intended to include both branched and  
15 straight-chain saturated aliphatic hydrocarbon groups  
having the specified number of carbon atoms, substituted  
with 1 or more halogen (for example  $-C_vF_w$  where  $v = 1$  to  $3$   
and  $w = 1$  to  $(2v+1)$ ). Examples of haloalkyl include, but  
are not limited to, trifluoromethyl, trichloromethyl,  
20 pentafluoroethyl, pentachloroethyl, 2,2,2-trifluoroethyl,  
heptafluoropropyl, and heptachloropropyl. Examples of  
haloalkyl also include "fluoroalkyl" which is intended to  
include both branched and straight-chain saturated  
aliphatic hydrocarbon groups having the specified number of  
25 carbon atoms, substituted with 1 or more fluorine atoms.

As used herein, "carbocycle" is intended to mean any  
stable 3, 4, 5, 6, or 7-membered monocyclic or bicyclic or  
7, 8, 9, 10, 11, 12, or 13-membered bicyclic or tricyclic,  
any of which may be saturated, partially unsaturated, or  
30 aromatic. Examples of such carbocycles include, but are  
not limited to, cyclopropyl, cyclobutyl, cyclopentyl,  
cyclohexyl, cycloheptyl, adamantyl, cyclooctyl,  
[3.3.0]bicyclooctane, [4.3.0]bicyclononane,  
[4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane,  
35 fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or  
tetrahydronaphthyl (tetralin).

As used herein, the term "heterocycle" or  
"heterocyclic group" is intended to mean a stable 5, 6, or  
7- membered monocyclic or bicyclic or 7, 8, 9, 10, 11, 12,  
40 13, or 14-membered bicyclic heterocyclic ring which is  
saturated partially unsaturated or unsaturated (ie.  
aromatic or "heteroaryl"), and which consists of carbon

5 atoms and 1, 2, 3 or 4 heteroatoms independently selected  
from the group consisting of N, O and S; and including any  
bicyclic group in which any of the above-defined  
heterocyclic rings is fused to a benzene ring. The  
nitrogen and sulfur heteroatoms may optionally be oxidized  
10 to -NO-, -SO-, or -SO<sub>2</sub>-. The heterocyclic ring may be  
attached to its pendant group at any heteroatom or carbon  
atom which results in a stable structure. The heterocyclic  
rings described herein may be substituted on carbon or on a  
nitrogen atom if the resulting compound is stable. If  
15 specifically noted, a nitrogen in the heterocycle may  
optionally be quaternized. It is preferred that when the  
total number of S and O atoms in the heterocycle exceeds 1,  
then these heteroatoms are not adjacent to one another. It  
is preferred that the total number of S and O atoms in the  
20 heterocycle is not more than 1.

Examples of heterocycles include, but are not limited  
to, 2-pyrrolidonyl, 2*H*,6*H*-1,5,2-dithiazinyl, 2*H*-pyrrolyl,  
3*H*-indolyl, 4-piperidonyl, 4*H*-quinolizinyl,  
6*H*-1,2,5-thiadiazinyl, acridinyl, azocinyl, benzimidazolyl,  
25 benzofuranyl, benzothiofuranyl, benzothiophenyl,  
benzoxazolyl, benzoxazoliny, benzthiazolyl, benztriazolyl,  
benztetrazolyl, benzisoxazolyl, benzisothiazolyl,  
benzimidazalonyl, carbazolyl, 4*aH*-carbazolyl,  $\beta$ -carbolinyl,  
chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl,  
30 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran,  
furanyl, furazanyl, imidazolidinyl, imidazoliny, imidazolyl,  
imidazolopyridinyl, 1*H*-indazolyl, indolenyl,  
indolinyl, indolizinyl, indolyl, isatinoyl,  
isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl,  
35 isoindolyl, isoquinolinyl, isothiazolyl,  
isothiazolopyridinyl, isoxazolyl, isoxazolopyridinyl,  
morpholinyl, naphthyridinyl, octahydroisoquinolinyl,  
oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl,  
1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl,  
40 oxazolyl, oxazolopyridinyl, oxazolidinylperimidinyl,  
oxindolyl, phenanthridinyl, phenanthrolinyl, phenarsazinyl,

5 phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl,  
 phthalazinyl, piperazinyl, piperidinyl, pteridinyl,  
 piperidonyl, 4-piperidonyl, pteridinyl, purinyl, pyranyl,  
 pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolopyridinyl,  
 pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole,  
 10 pyridothiazole, pyridinyl, pyridyl, pyrimidinyl,  
 pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl,  
 quinolinyl, 4*H*-quinolizinyll, quinoxalinyl, quinuclidinyl,  
 carbolinyl, tetrazolyl, tetrahydrofuranyl,  
 tetrahydroisoquinolinyl, tetrahydroquinolinyl,  
 15 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl,  
 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl,  
 thianthrenyl, thiazolyl, thiazolopyridinyl, thienyl,  
 thienothiazolyl, thienooxazolyl, thienoimidazolyl,  
 thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl,  
 20 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl.

Preferred 5 to 10 membered heterocycles include, but  
 are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl,  
 pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl,  
 imidazolidinyl, indolyl, tetrazolyl, isoxazolyl,  
 25 morpholinyl, oxazolyl, oxazolidinyl, tetrahydrofuranyl,  
 thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl,  
 triazolyl, benzimidazolyl, 1*H*-indazolyl, benzofuranyl,  
 benzothiofuranyl, benztetrazolyl, benzotriazolyl,  
 benzisoxazolyl, benzoxazolyl, oxindolyl, benzoxazolinyl,  
 30 benzthiazolyl, benzisothiazolyl, isatinoyl, isoquinolinyl,  
 octahydroisoquinolinyl, tetrahydroisoquinolinyl,  
 tetrahydroquinolinyl, isoxazolopyridinyl, quinazolinyl,  
 quinolinyl, isothiazolopyridinyl, thiazolopyridinyl,  
 oxazolopyridinyl, imidazolopyridinyl, and  
 35 pyrazolopyridinyl.

Preferred 5 to 6 membered heterocycles include, but  
 are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl,  
 pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl,  
 imidazolidinyl, indolyl, tetrazolyl, isoxazolyl,  
 40 morpholinyl, oxazolyl, oxazolidinyl, tetrahydrofuranyl,  
 thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, and

5 triazolyl. Also included are fused ring and spiro  
compounds containing, for example, the above heterocycles.

As used herein, the term "aryl", "C<sub>6</sub>-C<sub>10</sub> aryl" or  
"aromatic residue", is intended to mean an aromatic moiety  
containing, if specified, the specified number of carbon  
10 atoms. For example, aryl is phenyl, pyridinyl or naphthyl.  
Unless otherwise specified, "aryl", "C<sub>6</sub>-C<sub>10</sub> aryl" or  
"aromatic residue" may be unsubstituted or substituted with  
0 to 3 groups selected from H, OH, OCH<sub>3</sub>, Cl, F, Br, I, CN,  
NO<sub>2</sub>, NH<sub>2</sub>, N(CH<sub>3</sub>)H, N(CH<sub>3</sub>)<sub>2</sub>, CF<sub>3</sub>, OCF<sub>3</sub>, C(=O)CH<sub>3</sub>, SCH<sub>3</sub>,  
15 S(=O)CH<sub>3</sub>, S(=O)<sub>2</sub>CH<sub>3</sub>, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, CO<sub>2</sub>H, and CO<sub>2</sub>CH<sub>3</sub>.

The term "amino acid" as used herein means an organic  
compound containing both a basic amino group and an acidic  
carboxyl group. Included within this term are natural  
20 amino acids (e.g., L-amino acids), modified and unusual  
amino acids (e.g., D-amino acids), as well as amino acids  
which are known to occur biologically in free or combined  
form but usually do not occur in proteins. Included within  
this term are modified and unusual amino acids, such as  
25 those disclosed in, for example, Roberts and Vellaccio  
(1983) The Peptides, 5: 342-429, the teaching of which is  
hereby incorporated by reference. "Natural amino acids"  
include, but are not limited to, alanine, arginine,  
asparagine, aspartic acid, cysteine, glutamic acid,  
30 glutamine, glycine, histidine, isoleucine, leucine, lysine,  
methionine, phenylalanine, serine, threonine, tyrosine,  
tyrosine, tryptophan, proline, and valine. Natural  
non-protein amino acids include, but are not limited to  
arginosuccinic acid, citrulline, cysteine sulfinic acid,  
35 3,4-dihydroxyphenylalanine, homocysteine, homoserine,  
ornithine, 3-moniodotyrosine, 3,5-diiodotryosine,  
3,5,5'-triiodothyronine, and 3,3',5,5'-tetraiodothyronine.  
Modified or unusual amino acids which can be used to  
practice the invention include, but are not limited to,  
40 D-amino acids, hydroxylysine, 4-hydroxyproline, an  
N-CBZ-protected amino acid, 2,4-diaminobutyric acid,

5 homoarginine, norleucine, N-methylaminobutyric acid,  
 naphthylalanine, phenylglycine,  $\beta$ -phenylproline,  
 tert-leucine, 4-aminocyclohexylalanine,  
 N-methyl-norleucine, 3,4-dehydroproline,  
 N,N-dimethylaminoglycine, N-methylaminoglycine,  
 10 4-aminopiperidine-4-carboxylic acid, 6-aminocaproic acid,  
 trans-4-(aminomethyl)-cyclohexanecarboxylic acid, 2-, 3-,  
 and 4-(aminomethyl)-benzoic acid,  
 1-aminocyclopentanecarboxylic acid,  
 1-aminocyclopropanecarboxylic acid, and  
 15 2-benzyl-5-aminopentanoic acid.

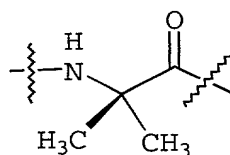
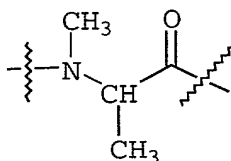
As used throughout the specification, the following  
 abbreviations for amino acid residues or amino acids apply:

Abu is L-aminobutyric acid;  
 20 Ala is L-alanine;  
 Alg is L-2-amino-4-pentenoic acid;  
 Ape is L-2-aminopentanoic acid;  
 Arg is L-arginine;  
 Asn is L-asparagine;  
 25 Asp is L-aspartic acid;  
 Aze is azedine-2-carboxylic acid;  
 Cha is L-2-amino-3-cyclohexylpropionic acid;  
 Cpa is L-2-amino-3-cyclopropylpropionic acid  
 Cpg is L-2-amino-2-cyclopropylacetic acid;  
 30 Cys is L-cysteine;  
 Dfb is L-4,4'-difluoro-1-amino-butyric acid;  
 Dpa is L-2-amino-3,3-diphenylpropionic acid  
 Gln is L-glutamine;  
 Glu is L-glutamic acid;  
 35 Gly is glycine;  
 His is L-histidine;  
 HomoLys is L-homolysine;  
 Hyp is L-4-hydroxyproline;  
 Ile is L-isoleucine;  
 40 Irg is isothiuronium analog of L-Arg;  
 Leu is L-leucine;  
 Lys is L-lysine;



5 Met is L-methionine;  
 Orn is L-ornithine;  
 Phe is L-phenylalanine;  
 Phe(4-fluoro) is para-fluorophenylalanine;  
 Pro is L-proline;  
 10 Sar is L-sarcosine;  
 Ser is L-serine;  
 Thr is L-threonine;  
 Tpa is L-2-amino-5,5,5-trifluoropentanoic acid;  
 Trp is L-tryptophan;  
 15 Tyr is L-tyrosine;  
 Val is L-valine; and  
 HyPOBn: O-benzyl hydroxylproline.

"Amino acid residue" as used herein, refers to  
 20 natural, modified or unnatural amino acids of either D- or  
 L-configuration and means an organic compound containing  
 both a basic amino group and an acidic carboxyl group.  
 Natural amino acids residues are Ala, Arg, Asn, Asp, Aze,  
 Cys, Gln, Glu, Gly, His, Hyp, Ile, Irg Leu, Lys, Met, Orn,  
 25 Phe, Phe(4-fluoro), Pro, Sar, Ser, Thr, Trp, Tyr, and Val.  
 Roberts and Vellaccio, The Peptides, Vol 5; 341-449 (1983),  
 Academic Press, New York, discloses numerous suitable  
 unnatural amino acids and is incorporated herein by  
 reference for that purpose. Additionally, said reference  
 30 describes, but does not extensively list, acyclic N-alkyl  
 and acyclic  $\alpha,\alpha$ -disubstituted amino acids. Included in the  
 scope of the present invention are N-alkyl, aryl, and  
 alkylaryl analogs of both in chain and N-terminal amino  
 acid residues. Similarly, alkyl, aryl, and alkylaryl maybe  
 35 substituted for the alpha hydrogen. Illustrated below are  
 examples of N-alkyl and alpha alkyl amino acid residues,  
 respectively.



Unnatural amino acids that fall within the scope of this invention are by way of example and without limitation:

2-aminobutanoic acid, 2-aminopentanoic acid, 2-aminohexanoic  
 10 acid, 2-aminoheptanoic acid, 2-aminooctanoic acid, 2-aminononanoic acid, 2-aminodecanoic acid, 2-aminoundecanoic acid, 2-amino-3,3-dimethylbutanoic acid, 2-amino-4,4-dimethylpentanoic acid, 2-amino-3-methylhexanoic acid, 2-amino-3-methylheptanoic acid, 2-amino-3-methyloctanoic  
 15 acid, 2-amino-3-methylnonanoic acid, 2-amino-4-methylhexanoic acid, 2-amino-3-ethylpentanoic acid, 2-amino-3,4-dimethylpentanoic acid, 2-amino-3,5-dimethylhexanoic acid, 2-amino-3,3-dimethylpentanoic acid, 2-amino-3-ethyl-3-methylpentanoic acid, 2-amino-3,3-diethylpentanoic acid, 2-amino-5-methylhexanoic acid, 2-amino-6-methylheptanoic, 2-amino-7-methyloctanoic, 2-amino-2-cyclopentylacetic, 2-amino-2-cyclohexylacetic acid, 2-amino-2-(1-methylcyclohexyl)acetic acid, 2-amino-2-(2-methyl-1-methylcyclohexyl)acetic acid, 2-amino-2-(3-methyl-1-methylcyclohexyl)acetic acid, 2-amino-2-(4-methyl-1-methylcyclohexyl)acetic acid, 2-amino-2-(1-ethylcyclohexyl)acetic acid, 2-amino-3-(cyclohexyl)propanoic acid, 2-amino-4-(cyclohexyl)butanoic acid, 2-amino-3-(1-adamantyl)propanoic acid, 2-amino-3-butenic acid, 2-amino-3-methyl-3-butenic acid, 2-amino-4-pentenoic acid, 2-amino-4-hexenoic acid, 2-amino-5-heptenoic acid, 2-amino-4-methyl-4-hexenoic acid, 2-amino-5-methyl-4-hexenoic acid, 2-amino-4-methyl-5-hexenoic acid, 2-amino-6-heptenoic acid, 2-amino-3,3,4-trimethyl-4-pentenoic acid, 2-amino-4-chloro-4-pentenoic, 2-amino-4,4-dichloro-3-butenic acid, 2-amino-3-(2-methylenecyclopropyl)-propanoic acid, 2-amino-2-(2-cyclopentenyl)acetic acid, 2-amino-2-(cyclohexenyl)acetic acid, 2-amino-3-(2-cyclopentenyl)propanoic acid, 2-amino-3-(3-cyclopentenyl)propanoic acid, 2-amino-3-(1-cyclohexyl)propanoic acid, 2-amino-2-(1-cyclopentenyl)acetic acid, 2-amino-2-(1-cyclohexyl)acetic

5 acid, 2-amino-2-(1-cycloheptenyl)acetic acid, 2-amino-2-(1-cyclooctenyl)acetic acid, 2-amino-3-(1-cycloheptenyl)propanoic acid, 2-amino-3-(1,4-cyclohexadienyl)propanoic acid, 2-amino-3-(2,5-cyclohexadienyl)propanoic acid, 2-amino-2-(7-cycloheptatrienyl)acetic acid, 2-amino-4,5-hexadienoic acid, 2-amino-3-butynoic acid, 2-amino-4-pentynoic acid, 2-amino-4-hexynoic acid, 2-amino-4-hepten-6-ynoic acid, 2-amino-3-fluoropropanoic acid, 2-amino-3,3,3-trifluoropropanoic acid, 2-amino-3-fluorobutanoic acid, 2-amino-3-fluoropentanoic acid, 2-amino-3-fluorohexanoic acid, 2-amino-3,3-difluorobutanoic acid, 2-amino-3,3-difluoro-3-phenylpropanoic acid, 2-amino-3-perfluoroethylpropanoic acid, 2-amino-3-perfluoropropylpropanoic acid, 2-amino-3-fluoro-3-methylbutanoic acid, 2-amino-5,5,5-trifluoropentanoic acid, 2-amino-3-methyl-4,4,4-trifluorobutanoic acid, 2-amino-3-trifluoromethyl-4,4,4-trifluorobutanoic acid, 2-amino-3,3,4,4,5,5-heptafluoropentanoic acid, 2-amino-3-methyl-5-fluoropentanoic acid, 2-amino-3-methyl-4-fluoropentanoic acid, 2-amino-5,5-difluorohexanoic acid, 2-amino-4-(fluoromethyl)-5-fluoropentanoic acid, 2-amino-4-trifluoromethyl-5,5,5-trifluoropentanoic acid, 2-amino-3-fluoro-3-methylbutanoic acid, 2-amino-3-fluoro-3-phenylpentanoic acid, 2-amino-2-(1-fluorocyclopentyl)acetic acid, 2-amino-2-(1-fluorocyclohexyl)acetic acid, 2-amino-3-chloropropanoic acid, 2-amino-3-chlorobutanoic acid, 2-amino-4,4-dichlorobutanoic acid, 2-amino-4,4,4-trichlorobutanoic acid, 2-amino-3,4,4-trichlorobutanoic acid, 2-amino-6-chlorohexanoic acid, 2-amino-4-bromobutanoic acid, 2-amino-3-bromobutanoic acid, 2-amino-3-mercaptopentanoic acid, 2-amino-4-mercaptopentanoic acid, 2-amino-3-mercapto-3,3-dimethylpropanoic acid, 2-amino-3-mercapto-3-methylpentanoic acid, 2-amino-3-mercaptopentanoic acid, 2-amino-3-mercapto-4-methylpentanoic acid, 2-amino-3-methyl-4-mercaptopentanoic acid, 2-amino-5-mercapto-5-methylhexanoic acid, 2-amino-2-(1-mercaptopocyclobutyl)acetic acid, 2-amino-2-(1-

- 5 mercaptocyclopentyl)acetic acid, 2-amino-2-(1-  
mercaptocyclohexyl)acetic acid, 2-amino-5-  
(methylthio)pentanoic acid, 2-amino-6-(methylthio)hexanoic  
acid, 2-amino-4-methylthio-3-phenylbutanoic acid, 2-amino-  
5-ethylthio-5-methylpentanoic acid, 2-amino-5-ethylthio-  
10 3,5,5-trimethylpentanoic acid, 2-amino-5-ethylthio-5-  
phenylpentanoic acid, 2-amino-5-ethylthio-5-pentanoic acid,  
2-amino-5-butylthio-5-methylpentanoic acid, 2-amino-5-  
butylthio-3,5,5-trimethylpentanoic acid, 2-amino-5-  
butylthio-5-phenylpentanoic acid, 2-amino-5-  
15 (butylthio)pentanoic acid, 2-amino-3-methyl-4-  
hydroselenopentanoic acid, 2-amino-4-methylselenobutanoic  
acid, 2-amino-4-ethylselenobutanoic acid, 2-amino-4-  
benzylselenobutanoic acid, 2-amino-3-methyl-4-  
(methylseleno)butanoic acid, 2-amino-3-  
20 (aminomethylseleno)propanoic acid, 2-amino-3-(3-  
aminopropylseleno)propanoic acid, 2-amino-4-  
methyltellurobutanoic acid, 2-amino-4-hydroxybutanoic acid,  
2-amino-4-hydroxyhexanoic acid, 2-amino-3-hydroxypentanoic  
acid, 2-amino-3-hydroxyhexanoic acid, 2-amino-3-methyl-4-  
25 hydroxybutanoic acid, 2-amino-3-hydroxy-3-methylbutanoic  
acid, 2-amino-6-hydroxyhexanoic acid, 2-amino-4-  
hydroxyhexanoic acid, 2-amino-3-hydroxy-4-methylpentanoic  
acid, 2-amino-3-hydroxy-3-methylpentanoic acid, 2-amino-4-  
hydroxy-3,3-dimethylbutanoic acid, 2-amino-3-hydroxy-4-  
30 methylpentanoic acid, 2-amino-3-hydroxybutanedioic acid, 2-  
amino-3-hydroxy-3-phenylpropanoic acid, 2-amino-3-hydroxy-  
3-(4-nitrophenyl)propanoic acid, 2-amino-3-hydroxy-3-(3-  
pyridyl)propanoic acid, 2-amino-2-(1-  
hydroxycyclopropyl)acetic acid, 2-amino-3-(1-  
35 hydroxycyclohexyl)propanoic acid, 2-amino-3-hydroxy-3-  
phenylpropanoic acid, 2-amino-3-hydroxy-3-[3-bis(2-  
chloroethyl)aminophenyl]propanoic acid, 2-amino-3-hydroxy-  
3-(3,4-dihydroxyphenyl)propanoic acid, 2-amino-3-hydroxy-3-  
(3,4-methylenedioxyphenyl)propanoic acid, 2-amino-4-fluoro-  
40 3-hydroxybutanoic acid, 2-amino-4,4,4-trichloro-3-  
hydroxybutanoic acid, 2-amino-3-hydroxy-4-hexynoic acid, 2-  
amino-3,4-dihydroxybutanoic acid, 2-amino-3,4,5,6-

5 tetrahydroxyhexanoic acid, 2-amino-4,5-dihydroxy-3-methylpentanoic acid, 2-amino-5,6-dihydroxyhexanoic acid, 2-amino-5-hydroxy-4-(hydroxymethyl)pentanoic acid, 2-amino-4,5-dihydroxy-4-(hydroxymethyl)pentanoic acid, 2-amino-3-hydroxy-5-benzoyloxypentanoic acid, 2-amino-3-(2-aminoethoxy)propanoic acid, 2-amino-4-(2-aminoethoxy)butanoic acid, 2-amino-4-oxobutanoic acid, 2-amino-3-oxobutanoic acid, 2-amino-4-methyl-3-oxopentanoic acid, 2-amino-3-phenyl-3-oxopropanoic acid, 2-amino-4-phenyl-3-oxobutanoic acid, 2-amino-3-methyl-4-oxopentanoic acid, 2-amino-4-oxo-4-(4-hydroxyphenyl)butanoic acid, 2-amino-4-oxo-4-(2-furyl)butanoic acid, 2-amino-4-oxo-4-(2-nitrophenyl)butanoic acid, 2-amino-4-oxo-4-(2-amino-4-chlorophenyl)butanoic acid, 2-amino-3-(4-oxo-1-cyclohexenyl)propanoic acid, 2-amino-3-(4-oxocyclohexenyl)propanoic acid, 2-amino-3-(2,5-dimethyl-3,6-dioxo-1,4-cyclohexadienyl)propanoic acid, 2-amino-3-(1-hydroxy-5-methyl-7-oxo-cyclohepta-1,3,5-trien-2-yl)propanoic acid, 2-amino-3-(1-hydroxy-7-oxo-cyclohepta-1,3,5-trien-3-yl)propanoic acid, 2-amino-3-(1-hydroxy-7-oxo-cyclohepta-1,3,5-trien-4-yl)propanoic acid, 2-amino-4-methoxy-3-butenic acid, 2-amino-4-(2-aminoethoxy)-3-butenic acid, 2-amino-4-(2-amino-3-hydroxypropyl)-3-butenic acid, 2-amino-2-(4-methoxy-1,4-cyclohexadienyl)acetic acid, 2-amino-3,3-diethoxypropanoic acid, 2-amino-4,4-dimethylbutanoic acid, 2-amino-2-(2,3-epoxycyclohexyl)acetic acid, 2-amino-3-(2,3-epoxycyclohexyl)propanoic acid, 2-amino-8-oxo-9,10-epoxydecanoic acid, 2-amino-propanedioic acid, 2-amino-3-methylbutanedioic acid, 2-amino-3,3-dimethylbutanedioic acid, 2-amino-4-methylpentanedioic acid, 2-amino-3-methylpentanedioic acid, 2-amino-3-phenylpentanedioic acid, 2-amino-3-hydroxypentanedioic acid, 2-amino-3-carboxypentanedioic acid, 2-amino-4-ethylpentanedioic acid, 2-amino-4-propylpentanedioic acid, 2-amino-4-isoamylpentanedioic acid, 2-amino-4-phenylpentanedioic acid, 2-amino-hexanedioic acid, 2-amino-heptanedioic acid, 2-amino-decanedioic acid, 2-amino-octanedioic acid, 2-

5 amino-dodecanedioic acid, 2-amino-3-methylenebutanedioic acid, 2-amino-4-methylenepentanedioic acid, 2-amino-3-fluorobutanedioic acid, 2-amino-4-fluoropentanedioic acid, 2-amino-3,3-difluorobutanedioic acid, 2-amino-3-chloropentanedioic acid, 2-amino-3-hydroxybutanedioic acid,  
 10 2-amino-4-hydroxypentanedioic acid, 2-amino-4-hydroxyhexanedioic acid, 2-amino-3,4-dihydroxypentanedioic acid, 2-amino-3-(3-hydroxypropyl)butanedioic acid, 2-amino-3-(1-carboxy-4-hydroxy-2-cyclodienyl)propanoic acid, 2-amino-3-(aceto)butanedioic acid, 2-amino-3-cyanobutanedioic acid, 2-amino-3-(2-carboxy-6-oxo-6H-pyranyl)propanoic acid,  
 15 2-amino-3-carboxybutanedioic acid, 2-amino-4-carboxypentanedioic acid, 3-amido-2-amino-3-hydroxypropanoic acid, 3-amido-2-amino-3-methylpropanoic acid, 3-amido-2-amino-3-phenylpropanoic acid, 3-amido-2,3-diaminopropanoic acid, 3-amido-2-amino-3-[N-(4-hydroxyphenyl)amino]propanoic acid, 2,3-diaminopropanoic acid, 2,3-diaminobutanoic acid, 2,4-diaminobutanoic acid, 2,4-diamino-3-methylbutanoic acid, 2,4-diamino-3-phenylbutanoic acid, 2-amino-3-(methylamino)butanoic acid,  
 25 2,5-diamino-3-methylpentanoic acid, 2,7-diaminoheptanoic acid, 2,4-diaminoheptanoic acid, 2-amino-2-(2-piperidyl)acetic acid, 2-amino-2-(1-aminocyclohexyl)acetic acid, 2,3-diamino-3-phenylpropanoic acid, 2,3-diamino-3-(4-hydroxyphenyl)propanoic acid, 2,3-diamino-3-(4-methoxyphenyl)propanoic acid, 2,3-diamino-3-[4-(N,N'-dimethylamino)phenyl]propanoic acid, 2,3-diamino-3-(3,4-dimethoxyphenyl)propanoic acid, 2,3-diamino-3-(3,4-methylenedioxyphenyl)propanoic acid, 2,3-diamino-3-(4-hydroxy-3-methoxyphenyl)propanoic acid, 2,3-diamino-3-(2-phenylethyl)propanoic acid, 2,3-diamino-3-propylpropanoic acid, 2,6-diamino-4-hexenoic acid, 2,5-diamino-4-fluoropentanoic acid, 2,6-diamino-5-fluorohexanoic acid, 2,6-diamino-4-hexynoic acid, 2,6-diamino-5,5-difluorohexanoic acid, 2,6-diamino-5,5-dimethylhexanoic acid, 2,5-diamino-3-hydroxypentanoic acid, 2,6-diamino-3-hydroxyhexanoic acid, 2,5-diamino-4-hydroxypentanoic acid, 2,6-diamino-4-hydroxyhexanoic acid, 2,6-diamino-4-

5 oxohexanoic acid, 2,7-diaminooctanedioic acid, 2,6-diamino-  
 3-carboxyhexanoic acid, 2,5-diamino-4-carboxypentanoic  
 acid, 2-amino-4-(2-(N,N'-diethylamino)ethyl)pentandioic  
 acid, 2-amino-4-(N,N'-diethylamino)pentandioic acid, 2-  
 amino-4-(N-morpholino)pentandioic acid, 2-amino-4-(N,N'-  
 10 bis(2-chloroethyl)amino)pentandioic acid, 2-amino-4-(N,N'-  
 bis(2-hydroxyethyl)amino)pentandioic acid, 2,3,5-  
 triaminopentanoic acid, 2-amino-3-(N-(2-  
 aminethyl)amino)propanoic acid, 2-amino-3-((2-  
 aminoethyl)seleno)propanoic acid, 2-amino-3-[(2-  
 15 aminoethyl)thio]propanoic acid, 2-amino-4-aminooxybutanoic  
 acid, 2-amino-5-hydroxyaminopentanoic acid, 2-amino-5-[N-  
 (5-nitro-2-pyrimidinyl)amino]pentanoic acid, 2-amino-4-[(7-  
 nitro-2,1,3-benzoxadiazol-4-yl)amino]butanoic acid, 2-  
 amino-3-guanidinopropanoic acid, 2-amino-3-  
 20 guanidinobutanoic acid, 2-amino-4-guanidobutanoic acid, 2-  
 amino-6-guanidohexanoic acid, 2-amino-6-ureidohexanoic  
 acid, 2-amino-3-(2-iminoimidiazolin-4-yl)propanoic acid, 2-  
 amino-2-(2-iminohexahydropyrimidin-4-yl)acetic acid, 2-  
 amino-3-(2-iminohexahydropyrimidin-4-yl)propanoic acid, 2-  
 25 amino-4-fluoro-5-guanidopentanoic acid, 2-amino-4-hydroxy-5-  
 guanidopentanoic acid, 2-amino-4-guanidooxybutanoic acid,  
 2-amino-6-amidinohexanoic acid, 2-amino-5-(N-  
 acetimidoylamino)pentanoic acid, 1-  
 aminocyclopropanecarboxylic acid, 1-amino-4-  
 30 ethylcyclopropanecarboxylic acid, 1-  
 aminocyclopentanecarboxylic acid, 1-  
 aminocyclopentanecarboxylic acid, 1-amino-2,2,5,5-  
 tetramethyl-cyclohexanecarboxylic acid, 1-  
 aminocydoheptanecarboxylic acid, 1-  
 35 aminocyclononanecarboxylic acid, 2-aminoindan-2-carboxylic  
 acid, 2-aminonorbornane-2-carboxylic acid, 2-amino-3-  
 phenylnorbornane-2-carboxylic acid, 3-  
 aminotetrahydrothiophene-3-carboxylic acid, 1-amino-1,3-  
 cyclohexanedicarboxylic acid, 3-aminopyrrolidine-3-  
 40 carboxylic acid, 1,4-diaminocyclohexanecarboxylic acid, 6-  
 alkoxy-3-amino-1,2,3,4-tetrahydrocarbazole-3-carboxylic  
 acid, 2-aminobenzobicyclo[2,2,2]octane-2-carboxylic acid,





- 5 ethylphenyl)propanoic acid, 2-amino-3-(4-phenylphenyl)propanoic acid, 2-amino-3-(4-benzylphenyl)propanoic acid, 2-amino-3-(3-fluorophenyl)propanoic acid, 2-amino-3-(4-methylphenyl)propanoic acid, 2-amino-3-(4-fluorophenyl)propanoic acid, 2-amino-3-(4-chlorophenyl)propanoic acid, 2-amino-3-(2-chlorophenyl)propanoic acid, 2-amino-3-(4-bromophenyl)propanoic acid, 2-amino-3-(2-bromophenyl)propanoic acid, 2-amino-3-(3-hydroxyphenyl)propanoic acid, 2-amino-3-(2-hydroxyphenyl)propanoic acid, 2-amino-3-(4-mercaptophenyl)propanoic acid, 2-amino-3-(3-trifluoromethylphenyl)propanoic acid, 2-amino-3-(3-hydroxyphenyl)propanoic acid, 2-amino-3-(4-hydroxyphenyl)propanoic acid, 2-amino-3-[4-(hydroxymethyl)phenyl]propanoic acid, 2-amino-3-[3-(hydroxymethyl)phenyl]propanoic acid, 2-amino-3-[3-(aminomethyl)phenyl]propanoic acid, 2-amino-3-(3-carboxyphenyl)propanoic acid, 2-amino-3-(4-nitrophenyl)propanoic acid, 2-amino-3-(4-aminophenyl)propanoic acid, 2-amino-3-(4-azidophenyl)propanoic acid, 2-amino-3-(4-cyanophenyl)propanoic acid, 2-amino-3-(4-acetophenyl)propanoic acid, 2-amino-3-(4-guanidinophenyl)propanoic acid, 2-amino-3-[4-(phenylazo)phenyl]propanoic acid, 2-amino-3-[4-(2-phenylethylenyl)phenyl]propanoic acid, 2-amino-3-(4-trialkylsilylphenyl)propanoic acid, 2-amino-3-(2,4-dimethylphenyl)propanoic acid, 2-amino-3-(2,3-dimethylphenyl)propanoic acid, 2-amino-3-(2,5-dimethylphenyl)propanoic acid, 2-amino-3-(3,5-dimethylphenyl)propanoic acid, 2-amino-3-(2,4,6-trimethylphenyl)propanoic acid, 2-amino-3-(3,4,5-trimethylphenyl)propanoic acid, 2-amino-3-(2,3,4,5,6-pentamethylphenyl)propanoic acid, 2-amino-3-(2,4,-difluorophenyl)propanoic acid, 2-amino-3-(3,4,-difluorophenyl)propanoic acid, 2-amino-3-(2,5,-

- 5    difluorophenyl)propanoic acid, 2-amino-3-(2,6,-  
      difluorophenyl)propanoic acid, 2-amino-3-(2,3,5,6-  
      tetrafluorophenyl)propanoic acid, 2-amino-3-(3,5-dichloro-  
      2,4,6-trifluorophenyl)propanoic acid, 2-amino-3-(2,3-  
      difluorophenyl)propanoic acid, 2-amino-3-(2,3-
- 10   bistrifluoromethylphenyl)propanoic acid, 2-amino-3-(2,4-  
      bistrifluoromethylphenyl)propanoic acid, 2-amino-3-(2-  
      chloro-5-trifluoromethylphenyl)propanoic acid, 2-amino-3-  
      (2,5-difluorophenyl)propanoic acid, 2-amino-3-(2,3,4,5,6-  
      pentafluorophenyl)propanoic acid, 2-amino-3-(2,3-
- 15   dibromophenyl)propanoic acid, 2-amino-3-(2,5-  
      dibromophenyl)propanoic acid, 2-amino-3-(3,4-  
      dibromophenyl)propanoic acid, 2-amino-3-(3,4,5-  
      triiodophenyl)propanoic acid, 2-amino-3-(2,3-  
      dihydroxyphenyl)propanoic acid, 2-amino-3-(2,5-
- 20   dihydroxyphenyl)propanoic acid, 2-amino-3-(2,6-  
      dihydroxyphenyl)propanoic acid, 2-amino-3-(3-bromo-5-  
      methoxyphenyl)propanoic acid, 2-amino-3-(2,5-  
      dimethoxyphenyl)propanoic acid, 2-amino-3-(2,5-dimethoxy-4-  
      methylphenyl)propanoic acid, 2-amino-3-(4-bromo-2,5-
- 25   dimethoxyphenyl)propanoic acid, 2-amino-3-(3-carboxy-4-  
      hydroxyphenyl)propanoic acid, 2-amino-3-(3-carboxy-4-  
      aminophenyl)propanoic acid, 2-amino-3-(2-hydroxy-5-  
      nitrophenyl)propanoic acid, 2-amino-3-(2-ethoxy-5-  
      nitrophenyl)propanoic acid, 2-amino-3-(3,4,5-
- 30   trimethoxyphenyl)propanoic acid, 2-amino-3-(4-azido-2-  
      nitrophenyl)propanoic acid, 2-amino-3-(2-hydroxy-5-  
      nitrophenyl)propanoic acid, 2-amino-3-(2,4-bis-  
      trimethylsilylphenyl)propanoic acid, 2-amino-3-(4-hydroxy-  
      3,5-di-t-butylphenyl)propanoic acid, 2-amino-3-(4-hydroxy-
- 35   3-benzylphenyl)propanoic acid, 2-amino-3-(4-hydroxy-3-  
      fluorophenyl)propanoic acid, 2-amino-3-(4-hydroxy-2,3,5,6-  
      tetrafluorophenyl)propanoic acid, 2-amino-3-(4-hydroxy-3,5-  
      dichlorophenyl)propanoic acid, 2-amino-3-(4-hydroxy-3-  
      iodophenyl)propanoic acid, 2-amino-3-(4-hydroxy-3,5-
- 40   diiodophenyl)propanoic acid, 2-amino-3-(4-hydroxy-2-  
      hydroxyphenyl)propanoic acid, 2-amino-3-(4-hydroxy-3-  
      hydroxymethylphenyl)propanoic acid, 2-amino-3-(4-hydroxy-2-

5 hydroxy-6-methylphenyl)propanoic acid, 2-amino-3-(4-  
 hydroxy-3-carboxyphenyl)propanoic acid, 2-amino-3-(4-  
 hydroxy-3,5-dinitrophenyl)propanoic acid, substituted  
 thyronines, 2-amino-3-(3,4-dihydroxy-2-  
 chlorophenyl)propanoic acid, 2-amino-3-(3,4-dihydroxy-2-  
 10 bromophenyl)propanoic acid, 2-amino-3-(3,4-dihydroxy-2-  
 fluorophenyl)propanoic acid, 2-amino-3-(3,4-dihydroxy-2-  
 nitrophenyl)propanoic acid, 2-amino-3-(3,4-dihydroxy-2-  
 methylphenyl)propanoic acid, 2-amino-3-(3,4-dihydroxy-2-  
 ethylphenyl)propanoic acid, 2-amino-3-(3,4-dihydroxy-2-  
 15 isopropylphenyl)propanoic acid, 2-amino-3-(2-t-butyl-4,5-  
 dihydroxyphenyl)propanoic acid, 2-amino-3-(3-fluoro-4,5-  
 dihydroxyphenyl)propanoic acid, 2-amino-3-(2-fluoro-4,5-  
 dihydroxyphenyl)propanoic acid, 2-amino-3-(2,5,6-trifluoro-  
 3,4-dihydroxyphenyl)propanoic acid, 2-amino-3-(2,6-dibromo-  
 20 3,4-dihydroxyphenyl)propanoic acid, 2-amino-3-(5,6-dibromo-  
 3,4-dihydroxyphenyl)propanoic acid, 2-amino-3-(2,4,5-  
 trihydroxyphenyl)propanoic acid, 2-amino-3-(2,3,4-  
 trihydroxyphenyl)propanoic acid, 2-amino-3-(3,4-dihydroxy-  
 5-methoxyphenyl)propanoic acid, 2-amino-3-methyl-3-  
 25 phenylpropanoic acid, 2-amino-3-ethyl-3-phenylpropanoic  
 acid, 2-amino-3-isopropyl-3-phenylpropanoic acid, 2-amino-  
 3-butyl-3-phenylpropanoic acid, 2-amino-3-benzyl-3-  
 phenylpropanoic acid, 2-amino-3-phenylethyl-3-  
 phenylpropanoic acid, 2-amino-3-(4-chlorophenyl)-3-  
 30 phenylpropanoic acid, 2-amino-3-(4-methoxyphenyl)-3-  
 phenylpropanoic acid, 2-amino-3,3-diphenylpropanoic acid,  
 2-amino-3-[4-(N,N-diethylamino)phenyl]heptanoic acid, 2-  
 amino-3-[4-(N,N-diethylamino)phenyl]pentanoic acid, 2-  
 amino-3-(3,4-dimethoxyphenyl)pentanoic acid, 2-amino-3-  
 35 (3,4-dihydroxyphenyl)pentanoic acid, 2-amino-3-methyl-3-  
 phenylbutanoic acid, 2-amino-3-ethyl-3-phenylpentanoic  
 acid, 2-amino-3-methyl-3-phenylpentanoic acid, 2-amino-3,3-  
 diphenylbutanoic acid, 2-amino-3-fluoro-3-phenylpropanoic  
 acid, 2-amino-3-methylene-3-phenylpropanoic acid, 2-amino-  
 40 3-methylmercapto-3-phenylpropanoic acid, 2-amino-4-  
 methylmercapto-4-phenylbutanoic acid, 2-amino-4-(3,4-  
 dihydroxyphenyl)butanoic acid, 2-amino-5-(4-

5 methoxyphenyl)pentanoic acid, 2-amino-4-phenylbutanoic  
 acid, 2-amino-5-phenylpentanoic acid, 2-amino-3,3-dimethyl-  
 5-phenylpentanoic acid, 2-amino-4-phenyl-3-butenic acid,  
 2-amino-4-phenoxybutanoic acid, 2-amino-5-phenoxybutanoic  
 acid, 2-amino-2-(indanyl)acetic acid, 2-amino-2-(1-  
 10 tetralyl)acetic acid, 2-amino-4,4-diphenylbutanoic acid, 2-  
 amino-2-(2-naphthyl)acetic acid, 2-amino-3-(1-  
 naphthyl)propanoic acid, 2-amino-3-(1-naphthyl)pentanoic  
 acid, 2-amino-3-(2-naphthyl)propanoic acid, 2-amino-3-(1-  
 chloro-2-naphthyl)propanoic acid, 2-amino-3-(1-bromo-2-  
 15 naphthyl)propanoic acid, 2-amino-3-(4-hydroxy-1-  
 naphthyl)propanoic acid, 2-amino-3-(4-methoxy-1-  
 naphthyl)propanoic acid, 2-amino-3-(4-hydroxy-2-chloro-1-  
 naphthyl)propanoic acid, 2-amino-3-(2-chloro-4-methoxy-1-  
 naphthyl)propanoic acid, 2-amino-2-(2-anthryl)acetic acid,  
 20 2-amino-3-(9-anthryl)propanoic acid, 2-amino-3-(2-  
 fluorenyl)propanoic acid, 2-amino-3-(4-fluorenyl)propanoic  
 acid, 2-amino-3-(carboranyl)propanoic acid, 3-  
 methylproline, 4-methylproline, 5-methylproline, 4,4-  
 dimethylproline, 4-fluoroproline, 4,4-difluoroproline, 4-  
 25 bromoproline, 4-chloroproline, 4-aminoproline, 3,4-  
 dehydroproline, 4-methylproline, 4-methyleneproline, 4-  
 mercaptoproline, 4-(4-methoxybenzylmercapto)proline, 4-  
 hydroxymethylproline, 3-hydroxyproline, 3-hydroxy-5-  
 methylproline, 3,4-dihydroxyproline, 3-phenoxyproline, 2-  
 30 aminoproline, 5-aminoproline, 3-carbamylalkylproline, 4-  
 cyano-5-methyl-5-carboxyproline, 4,5-dicarboxyl-5-  
 methylproline, 2-aziridinecarboxylic acid, 2-  
 azetidinedicarboxylic acid, 4-methyl-2-azetidinedicarboxylic  
 acid, pipecolic acid, 1,2,3,6-tetrahydropicolinic acid,  
 35 3,4-methyleneproline, 2,4-methyleneproline, 4-  
 aminopipecolic acid, 5-hydroxypipecolic acid, 4,5-  
 dihydroxypipecolic acid, 5,6-dihydroxy-2,3-dihydroindole-2-  
 carboxylic acid, 1,2,3,4-tetrahydroquinoline-2-carboxylic  
 acid, 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline-3-  
 40 carboxylic acid, 6-hydroxy-1-methyl-1,2,3,4-  
 tetrahydroisoquinoline-3-carboxylic acid, 6,7-dihydroxy-1-  
 methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid,

5 1,3-oxazolidine-4-carboxylic acid, 1,2-oxazolidine-3-  
 carboxylic acid, perhydro-1,4-thiazine-3-carboxylic acid,  
 2,2-dimethylthiazolidine-4-carboxylic acid, perhydro-1,3-  
 thiazine-2-carboxylic acid, selenazolidine-4-carboxylic  
 acid, 2-phenylthiazolidine-4-carboxylic acid, 2-(4-  
 10 carboxylicyl)thiazolidine-4-carboxylic acid, 1,2,3,4,4a,9a-  
 hexahydro-beta-carboline-3-carboxylic acid, 2,3,3a,8a-  
 tetrahydropyrrolo(2,3b)indole-2-carboxylic acid, 2-amino-3-  
 (2-pyridyl)propanoic acid, 2-amino-3-(3-pyridyl)propanoic  
 acid, 2-amino-3-(4-pyridyl)propanoic acid, 2-amino-3-(2-  
 15 bromo-3-pyridyl)propanoic acid, 2-amino-3-(2-bromo-4-  
 pyridyl)propanoic acid, 2-amino-3-(2-bromo-5-  
 pyridyl)propanoic acid, 2-amino-3-(2-bromo-6-  
 pyridyl)propanoic acid, 2-amino-3-(2-chloro-3-  
 pyridyl)propanoic acid, 2-amino-3-(2-chloro-4-  
 20 pyridyl)propanoic acid, 2-amino-3-(2-chloro-5-  
 pyridyl)propanoic acid, 2-amino-3-(2-chloro-6-  
 pyridyl)propanoic acid, 2-amino-3-(2-fluoro-3-  
 pyridyl)propanoic acid, 2-amino-3-(2-fluoro-4-  
 pyridyl)propanoic acid, 2-amino-3-(2-fluoro-5-  
 25 pyridyl)propanoic acid, 2-amino-3-(2-fluoro-6-  
 pyridyl)propanoic acid, 2-amino-3-(1,2-dihydro-2-oxo-3-  
 pyridyl)propanoic acid, 2-amino-3-(1,2-dihydro-2-oxo-4-  
 pyridyl)propanoic acid, 2-amino-3-(1,2-dihydro-2-oxo-5-  
 pyridyl)propanoic acid, 2-amino-3-(1,2-dihydro-2-oxo-6-  
 30 pyridyl)propanoic acid, 2-amino-3-(5-hydroxy-2-  
 pyridyl)propanoic acid, 2-amino-3-(5-hydroxy-6-iodo-2-  
 pyridyl)propanoic acid, 2-amino-3-(3-hydroxy-4-oxo-  
 1,4dihydro-1-pyridyl)propanoic acid, N-(5-carboxyl-5-  
 aminopentyl)pyridinium chloride, 1,2,5-trimethyl-4-(2-  
 35 amino-2-carboxy-1-hydroxyethyl)pyridinium chloride, 2-  
 amino-2-(5-chloro-2-pyridyl)acetic acid, N-(3-amino-3-  
 carboxypropyl)pyridinium chloride, 2-amino-3-(2-  
 pyrrolyl)propanoic acid, 2-amino-3-(1-pyrrolyl)propanoic acid,  
 2-amino-4-(1-pyrrolyl)butanoic acid, 2-amino-5-(1-  
 40 pyrrolyl)pentanoic acid, 2-amino-3-(5-imidazolyl)-3-  
 methylpropanoic acid, 2-amino-3-(5-imidazolyl)-3-  
 ethylpropanoic acid, 2-amino-3-hexyl-3-(5-

- 5 imidazolyl)propanoic acid, 2-amino-3-hydroxy-3-(5-imidazolyl)propanoic acid, 2-amino-3-(4-nitro-5-imidazolyl)propanoic acid, 2-amino-3-(4-methyl-5-imidazolyl)propanoic acid, 2-amino-3-(2-methyl-5-imidazolyl)propanoic acid, 2-amino-3-(4-fluoro-5-imidazolyl)propanoic acid, 2-amino-3-(2-fluoro-5-imidazolyl)propanoic acid, 2-amino-3-(2-amino-5-imidazolyl)propanoic acid, 2-amino-3-(2-phenylaza-5-imidazolyl)propanoic acid, 2-amino-3-(1-methyl-2-nitro-5-imidazolyl)propanoic acid, 2-amino-3-(1-methyl-4-nitro-5-imidazolyl)propanoic acid, 2-amino-3-(1-methyl-5-nitro-5-imidazolyl)propanoic acid, 2-amino-3-(2-mercapto-5-imidazolyl)propanoic acid, 2-amino-4-(5-imidazolyl)butanoic acid, 2-amino-3-(1-imidazolyl)propanoic acid, 2-amino-3-(2-imidazolyl)propanoic acid, 2-amino-(1-pyrazolyl)propanoic acid, 2-amino-(3-pyrazolyl)propanoic acid, 2-amino-(3,5-dialkyl-4-pyrazolyl)propanoic acid, 2-amino-3-(3-amino-1,2,4-triazol-1-yl)propanoic acid, 2-amino-3-(tetrazol-5-yl)propanoic acid, 2-amino-4-(5-tetrazolyl)butanoic acid, 2-amino-3-(6-methyl-3-indolyl)propanoic acid, 2-amino-3-(4-fluoro-3-indolyl)propanoic acid, 2-amino-3-(5-fluoro-3-indolyl)propanoic acid, 2-amino-3-(6-fluoro-3-indolyl)propanoic acid, 2-amino-3-(4,5,6,7-tetrafluoro-3-indolyl)propanoic acid, 2-amino-3-(5-chloro-3-indolyl)propanoic acid, 2-amino-3-(6-chloro-3-indolyl)propanoic acid, 2-amino-3-(7-chloro-3-indolyl)propanoic acid, 2-amino-3-(5-bromo-3-indolyl)propanoic acid, 2-amino-3-(7-bromo-3-indolyl)propanoic acid, 2-amino-3-(2-hydroxy-3-indolyl)propanoic acid, 2-amino-3-(5-hydroxy-3-indolyl)propanoic acid, 2-amino-3-(7-hydroxy-3-indolyl)propanoic acid, 2-amino-3-(2-alkylmercapto-3-indolyl)propanoic acid, 2-amino-3-(7-amino-3-indolyl)propanoic acid, 2-amino-3-(4-nitro-3-indolyl)propanoic acid, 2-amino-3-(7-nitro-3-indolyl)propanoic acid, 2-amino-3-(4-carboxy-3-indolyl)propanoic acid, 2-amino-3-(3-indolyl)butanoic acid, 2-amino-3-(2,3-dihydro-3-indolyl)propanoic acid, 2-amino-3-

5 (2,3-dihydro-2-oxo-3-indolyl)propanoic acid, 2-amino-3-alkylmercapto-3-(3-indolyl)propanoic acid, 2-amino-3-(4-aza-3-indolyl)propanoic acid, 2-amino-3-(7-aza-3-indolyl)propanoic acid, 2-amino-3-(7-aza-6-chloro-4-methyl-3-indolyl)propanoic acid, 2-amino-3-(2,3-dihydrobenzofuran-3-yl)propanoic acid, 2-amino-3-(3-methyl-5-7-dialkylbenzofuran-2-yl)propanoic acid, 2-amino-3-(benzothiophen-3-yl)propanoic acid, 2-amino-3-(5-hydroxybenzothiophen-3-yl)propanoic acid, 2-amino-3-eoenzoselenol-3yl)propanoic acid, 2-amino-3-quinolylpropanoic acid, 2-amino-3-(8-hydroxy-5-quinolyl)propanoic acid, 2-amino-2-(5,6,7,8-tetrahydroquinol-5-yl)acetic acid, 2-amino-3-(3-coumarinyl)propanoic acid, 2-amino-2-(benzisoxazol-3-yl)acetic acid, 2-amino-2-(5-methylbenzisoxazol-3-yl)acetic acid, 2-amino-2-(6-methylbenzisoxazol-3-yl)acetic acid, 2-amino-2-(7-methylbenzisoxazol-3-yl)acetic acid, 2-amino-2-(5-bromobenzisoxazol-3-yl)acetic acid, 2-amino-3-(benzimidazol-2-yl)propanoic acid, 2-amino-3-(5,6-dichlorobenzimidazol-2-yl)propanoic acid, 2-amino-3-(5,6-dimethylbenzimidazol-2-yl)propanoic acid, 2-amino-3-(4,5,6,7-hydrobenzirnidazol-2-yl)propanoic acid, 2-amino-2-(benzimidazol-5-yl)acetic acid, 2-amino-2-(1,3-dihydro-2,2-dioxoisobenzothiophen-5-yl)acetic acid, 2-amino-2-(1,3-dihydro-2,2-dioxo-2,1,3-benzothiadiazol-5-yl)acetic acid, 2-amino-2-(2-oxobenzimidazol-5-yl)acetic acid, 2-amino-3-(4-hydroxybenzothiazol-6-yl)propanoic acid, 2-amino-3-(benzoxazol-2-yl)propanoic acid, 2-amino-3-(benzothiazol-2-yl)propanoic acid, 2-amino-3-(9-adeninyl)propanoic acid, 2-amino-2-(6-chloro-9-purinyl)acetic acid, 2-amino-2-(6-amino-9-purinyl)acetic acid, 2-amino-3-(6-purinyl)propanoic acid, 2-amino-3-(8-theobrominyl)propanoic acid, 2-amino-2-(1-uracilyl)acetic acid, 2-amino-2-(1-cytosinyl)acetic acid, 2-amino-3-(1-uracilyl)propanoic acid, 2-amino-3-(1-cytosinyl)propanoic acid, 2-amino-4-(1-pyrimidinyl)butanoic acid, 2-amino-4-(4-amino-1-pyrimidinyl)butanoic acid, 2-amino-4-(4-hydroxy-1-pyrimidinyl)butanoic acid, 2-amino-5-(1-pyrimidinyl)pentanoic acid, 2-amino-5-(4-amino-1-

5 pyrimidinyl)pentanoic acid, 2-amino-5-(4-hydroxy-1-  
 pyrimidinyl)pentanoic acid, 2-amino-3-(5-  
 pyrimidinyl)propanoic acid, 2-amino-3-(6-uracilyl)propanoic  
 acid, 2-amino-3-(2-pyrimidinyl)propanoic acid, 2-amino-3-  
 (6-amino-4-chloro-2-pyrimidinyl)propanoic acid, 2-amino-3-  
 10 (4-hydroxy-2-pyrimidinyl)propanoic acid, 2-amino-3-(2-  
 amino-4-pyrimidinyl)propanoic acid, 2-amino-3-(4,5-  
 dihydroxypyrimidin-2-yl)propanoic acid, 2-amino-3-(2-  
 thiouracil-6-yl)propanoic acid, 2-amino-2-(5-alkyl-2-  
 tetrahydrofuryl)acetic acid, 2-amino-2-(5-methyl-2,5-  
 15 dihydro-2-furyl)acetic acid, 2-amino-2-(5-alkyl-2-  
 furyl)acetic acid, 2-amino-2-(2-furyl)acetic acid, 2-amino-  
 2-(3-hydroxy-5-methyl-4-isoxazolyl)acetic acid, 2-amino-3-  
 (4-bromo-3-hydroxy-5-isoxazolyl)propanoic acid, 2-amino-3-  
 (4-methyl-3-hydroxy-5-isoxazolyl)propanoic acid, 2-amino-3-  
 20 (3-hydroxy-5-isoxazolyl)propanoic acid, 2-amino-2-(3-  
 chloro-D2 -isoxazolin-5-yl)acetic acid, 2-amino-2-(3-oxo-5-  
 isoxazolidinyl)acetic acid, 2-amino-3-(3,5-dioxo-1,2,4-  
 oxadiazolin-2-yl)propanoic acid, 2-amino-3-(3-phenyl-5-  
 isoxazolyl)propanoic acid, 2-amino-3-[3-(4-hydroxyphenyl)-  
 25 1,2,4-oxadiazol-5-yl]propanoic acid, 2-amino-3-(2-  
 thienyl)propanoic acid, 2-amino-2-(2-furyl)acetic acid, 2-  
 amino-2-(2-thienyl)acetic acid, 2-amino-2-(2-  
 thiazolyl)acetic acid, 2-amino-3-(2-thiazolyl)propanoic  
 acid, 2-amino-4-(4-carboxy-2-thiazolyl)butanoic acid, 2-  
 30 amino-3-(4-thiazolyl)propanoic acid, 2-amino-3-(2-  
 selenolyl)propanoic acid, 2-amino-3-(2-amino-4-  
 selenolyl)propanoic acid, and  
 2-amino-3-(beta-ribofuranosyl)propanoic acid.

"Amino acids residue" also refers to various amino  
 35 acids where sidechain functional groups are coupled with  
 appropriate protecting groups known to those skilled in the  
 art. "The Peptides", Vol 3, 3-88 (1981)discloses numerous  
 suitable protecting groups and is incorporated herein by  
 reference for that purpose. Examples of amino acids where  
 40 sidechain functional groups are coupled with appropriate  
 protecting groups include, but are not limited to,  
 Asp(OMe), Glu(OMe), Hyp(OMe), Asp(O<sup>t</sup>Bu), Glu(O<sup>t</sup>Bu),



5 Hyp(O<sup>t</sup>Bu), Thr(O<sup>t</sup>Bu), Asp(OBzl), Glu(OBzl), Hyp(OBzl), and  
Thr(OBzl).

The phrase "pharmaceutically acceptable" is employed  
herein to refer to those compounds, materials,  
10 compositions, and/or dosage forms which are, within the  
scope of sound medical judgment, suitable for use in  
contact with the tissues of human beings and animals  
without excessive toxicity, irritation, allergic response,  
or other problem or complication, commensurate with a  
15 reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts"  
refer to derivatives of the disclosed compounds wherein the  
parent compound is modified by making acid or base salts  
thereof. Examples of pharmaceutically acceptable salts  
20 include, but are not limited to, mineral or organic acid  
salts of basic groups such as amines; and alkali or organic  
salts of acidic groups such as carboxylic acids. The  
pharmaceutically acceptable salts include the conventional  
non-toxic salts or the quaternary ammonium salts of the  
25 parent compound formed, for example, from non-toxic  
inorganic or organic acids. For example, such conventional  
non-toxic salts include those derived from inorganic acids  
such as hydrochloric, hydrobromic, sulfuric, sulfamic,  
phosphoric, and nitric; and the salts prepared from organic  
30 acids such as acetic, propionic, succinic, glycolic,  
stearic, lactic, malic, tartaric, citric, ascorbic, pamoic,  
maleic, hydroxymaleic, phenylacetic, glutamic, benzoic,  
salicylic, sulfanilic, 2-acetoxybenzoic, fumaric,  
toluenesulfonic, methanesulfonic, ethane disulfonic,  
35 oxalic, and isethionic.

The pharmaceutically acceptable salts of the present  
invention can be synthesized from the parent compound which  
contains a basic or acidic moiety by conventional chemical  
methods. Generally, such salts can be prepared by reacting  
40 the free acid or base forms of these compounds with a  
stoichiometric amount of the appropriate base or acid in  
water or in an organic solvent, or in a mixture of the two;

5 generally, nonaqueous media like ether, ethyl acetate,  
ethanol, isopropanol, or acetonitrile are preferred. Lists  
of suitable salts are found in *Remington's Pharmaceutical*  
*Sciences*, 17th ed., Mack Publishing Company, Easton, PA,  
1985, p. 1418, the disclosure of which is hereby  
10 incorporated by reference.

Since prodrugs are known to enhance numerous desirable  
qualities of pharmaceuticals (e.g., solubility,  
bioavailability, manufacturing, etc.) the compounds of the  
present invention may be delivered in prodrug form. Thus,  
15 the present invention is intended to cover prodrugs of the  
presently claimed compounds, methods of delivering the same  
and compositions containing the same. "Prodrugs" are  
intended to include any covalently bonded carriers which  
release an active parent drug of the present invention *in*  
20 *vivo* when such prodrug is administered to a mammalian  
subject. Prodrugs of the present invention are prepared by  
modifying functional groups present in the compound in such  
a way that the modifications are cleaved, either in routine  
manipulation or *in vivo*, to the parent compound. Prodrugs  
25 include compounds of the present invention wherein a  
hydroxy, amino, or sulfhydryl group is bonded to any group  
that, when the prodrug of the present invention is  
administered to a mammalian subject, it cleaves to form a  
free hydroxyl, free amino, or free sulfhydryl group,  
30 respectively. Examples of prodrugs include, but are not  
limited to, acetate, formate and benzoate derivatives of  
alcohol and amine functional groups in the compounds of the  
present invention.

"Stable compound" and "stable structure" are meant to  
35 indicate a compound that is sufficiently robust to survive  
isolation to a useful degree of purity from a reaction  
mixture, and formulation into an efficacious therapeutic  
agent.

"Therapeutically effective amount" is intended to  
40 include an amount of a compound of the present invention or  
an amount of the combination of compounds claimed effective  
to inhibit HCV infection or treat the symptoms of HCV

5 infection in a host. The combination of compounds is preferably a synergistic combination. Synergy, as described for example by Chou and Talalay, *Adv. Enzyme Regul.* **1984**, 22, 27-55, occurs when the effect (in this case, inhibition of the desired target) of the compounds  
10 when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at suboptimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity,  
15 increased antiviral effect, or some other beneficial effect of the combination compared with the individual components.

#### SYNTHESIS

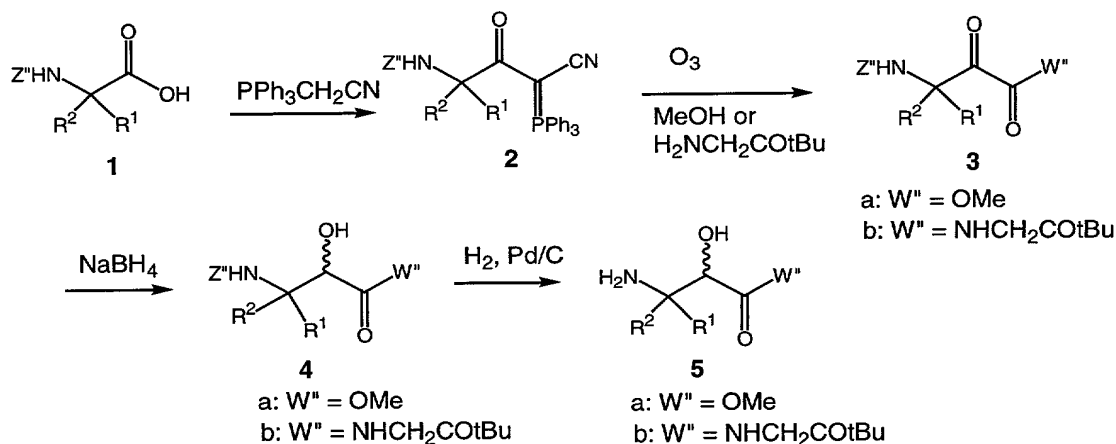
20 The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as  
25 appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. All references cited herein are hereby incorporated in their entirety herein by reference.

30 The novel compounds of this invention may be prepared using the reactions and techniques described in this section. The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in  
35 the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, are chosen to be the  
40 conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is

5 understood by one skilled in the art of organic synthesis  
that the functionality present on various portions of the  
molecule must be compatible with the reagents and reactions  
proposed. Such restrictions to the substituents which are  
compatible with the reaction conditions will be readily  
10 apparent to one skilled in the art and alternate methods  
must then be used.

A series of  $\alpha$ -hydroxyesters and  $\alpha$ -hydroxyamides of  
formula 5 are prepared by the method outlined in Scheme 1.  
Amino acid 1, wherein Z" is an amino protecting group, is  
15 treated with (cyanomethylene)triphenylphosphorane to give  
cyano keto phosphorane 2. Ozonolysis of 2 provides  $\alpha$ -  
ketoester 3a or  $\alpha$ -ketoamide 3b, which under reduction  
conditions yields  $\alpha$ -hydroxyester 4a or  $\alpha$ -hydroxyamide 4b.  
Hydrogenation of 4 in the presence of 10% Pd/C affords  $\alpha$ -  
20 hydroxyester 5a or  $\alpha$ -hydroxyamide 5b. (Wasserman, H. H. et  
al, J. Org. Chem. 1994, 59, 4364).

Scheme 1

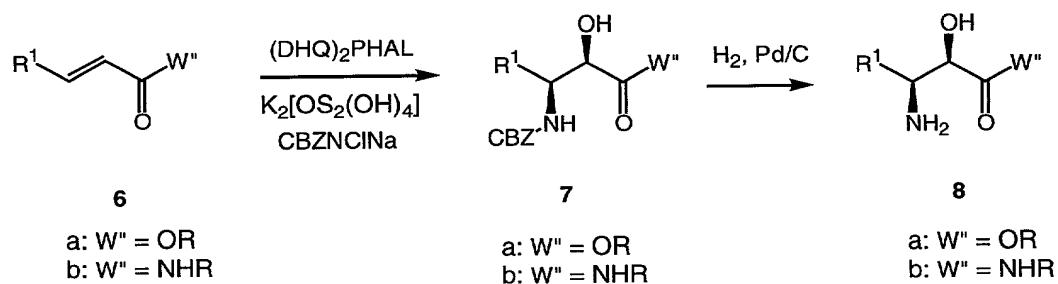


25

A series of  $\alpha$ -hydroxyl  $\beta$ -amino esters and  $\alpha$ -hydroxyl  
 $\beta$ -amino amides of formula 8 are prepared by the method  
outlined in Scheme 2. Many of the  $\alpha,\beta$ -unsaturated esters  
30 or amides 6 are commercially available or may be easily

5 prepared from commercially available materials. Sharpless  
 asymmetric aminohydroxylation of  $\alpha,\beta$ -unsaturated ester or  
 amide **6** gives  $\alpha$ -hydroxyl  $\beta$ -amino ester or  $\alpha$ -hydroxyl  $\beta$ -  
 amino amide **7**. Reductive removal of the carbobenzyloxy  
 (CBZ) group provides **8**. (Sharpless, K. B.; et al, *Angew.*  
 10 *Chem. Int. Ed. Engl.* **1996**, 35, 451. Sharpless, K. B. et  
 al, *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 2813.)

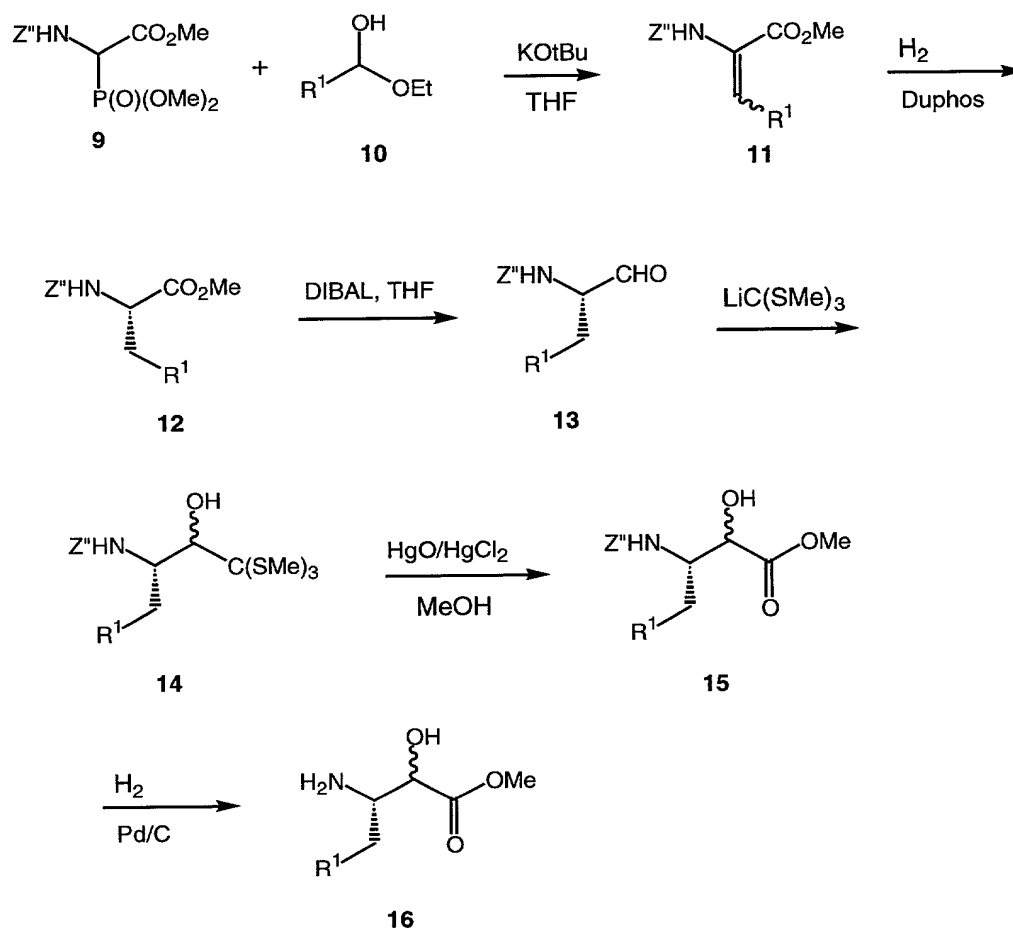
Scheme 2



15

A series of  $\alpha$ -hydroxyl  $\beta$ -amino esters of formula **15**  
 are prepared by the method outlined in Scheme 3. Treatment  
 of phosphonoglycine trimethyl ester **9**, wherein  $Z''$  is an  
 amino protecting group such as CBZ, with  
 20 difluoroacetaldehyde hemiacetal **10** in the presence of  $KOtBu$   
 yields  $\alpha,\beta$ -unsaturated ester **11**. Hydrogenation of **11** in  
 the presence of a chiral Rh catalyst, such as Duphos,  
 selectively reduces the double bond and affords **12** in high  
 enantiomeric excess. DIBAL reduction of methyl ester **12**  
 25 gives corresponding aldehyde **13**, which under the treatment  
 of lithium tris(methylthio)methane to provide  $\alpha$ -hydroxyl  
 compound **14**. Finally,  $\alpha$ -hydroxyl  $\beta$ -amino ester of formula  
**15** is obtained when **14** is treated with  $Hg^{2+}$ . (Kaneko, S.  
 K.; et al, *J. Org. Chem.* **1993**, 58, 2302.)

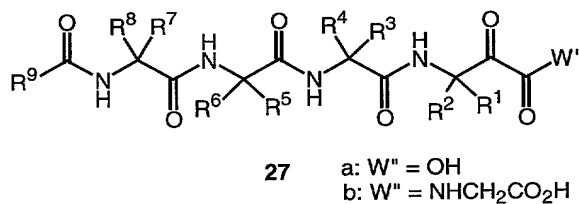
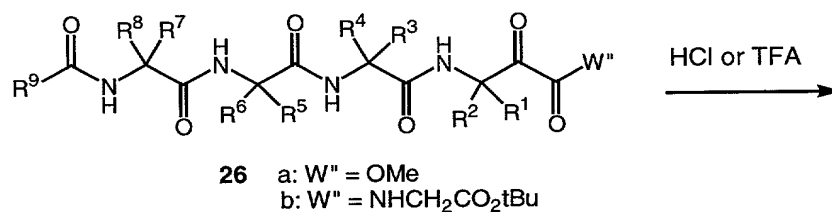
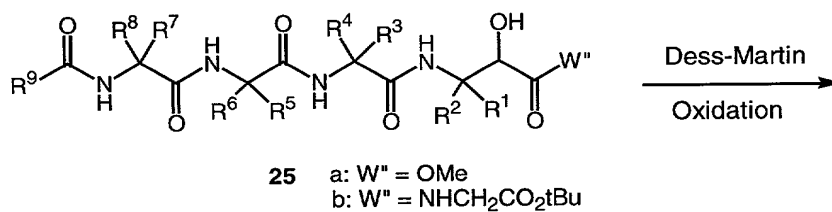
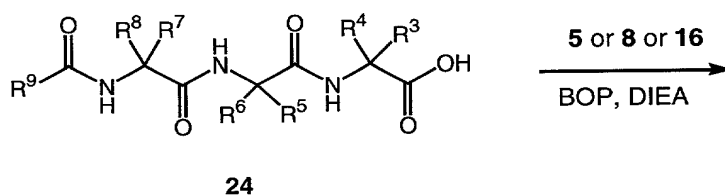
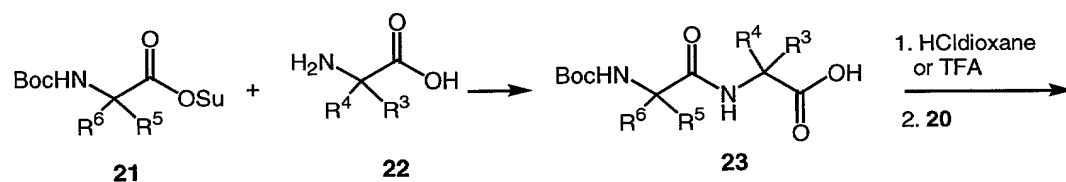
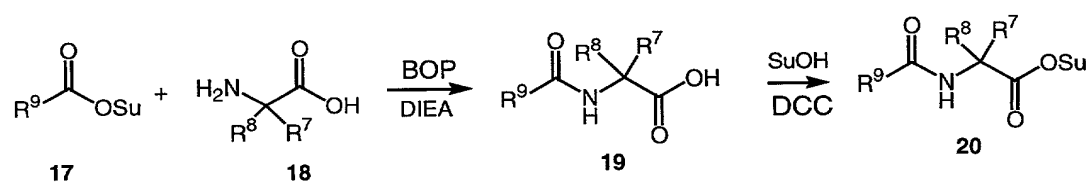
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A series of  $\alpha$ -ketoamides or acids of formula **27** are prepared by the method outlined in Scheme 4. Amino acid **18** is coupled with **17** under regular coupling conditions to afford **19**, which is then converted to its succinimide **20**. Compound **20** is coupled with dipeptide **23**, which is prepared by the same method, to yield tripeptide **24**. Compound **24** is reacted with the  $\alpha$ -hydroxyl  $\beta$ -amino ester or amide under standard coupling conditions to give  $\alpha$ -hydroxyl ester or amide **25**. Dess-Martin oxidation converts **25** to  $\alpha$ -keto ester or amide **26**. The methyl ester **26** is either saponified to provide  $\alpha$ -keto acid **27a**, or deprotected in

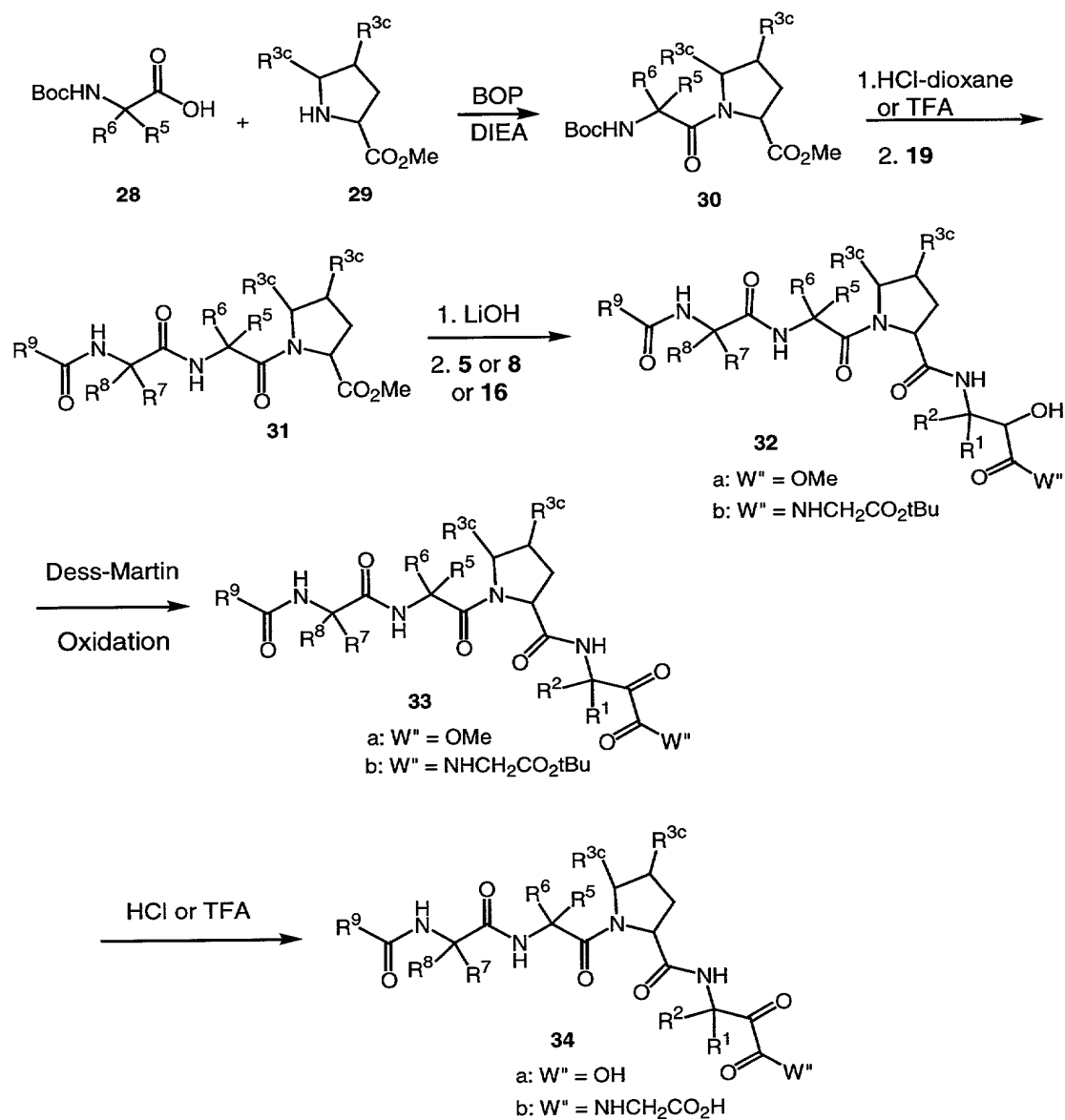
- 5 TFA to afford  $\alpha$ -keto amide **27b**. (Angelastro, M. R. *J. Med. Chem.* **1990**, 33, 13.)

Scheme 4



5 A series of  $\alpha$ -keto amides or acids of formula **34** are prepared by the method outlined in Scheme 5. Coupling of acid **28** with proline derivative **29** in the presence of BOP and DIEA yields compound **30**. Deprotection of BOC group in **30** followed by the coupling with the same intermediate **19** provides compound **31**. Application of similar chemistry to that described in Scheme 4 leads to the synthesis of  $\alpha$ -keto amides or acids of formula **34**.

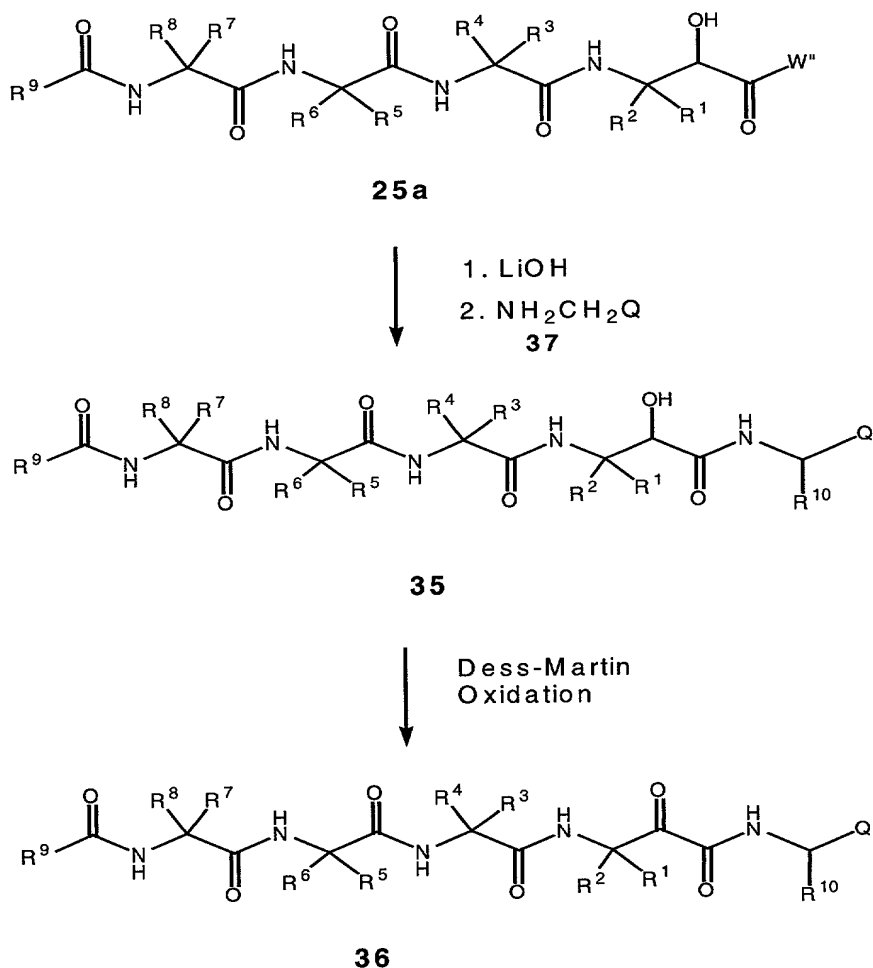
Scheme 5





5        A series of  $\alpha$ -ketoamides of formula **36** are prepared by  
the method outlined in Scheme 6. From the same  
intermediate **25a**, saponification affords the corresponding  
acid, which reacts with amines of formula **37** to give  $\alpha$ -  
hydroxyamide **35**. Dess-Martin oxidation of **35** provides  $\alpha$ -  
10 ketoamide **36**.

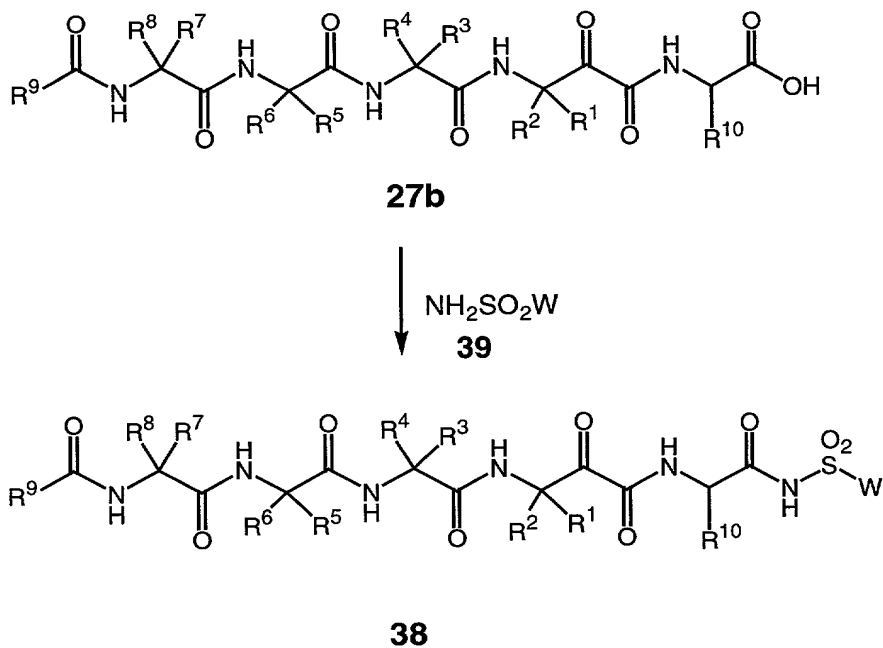
Scheme 6



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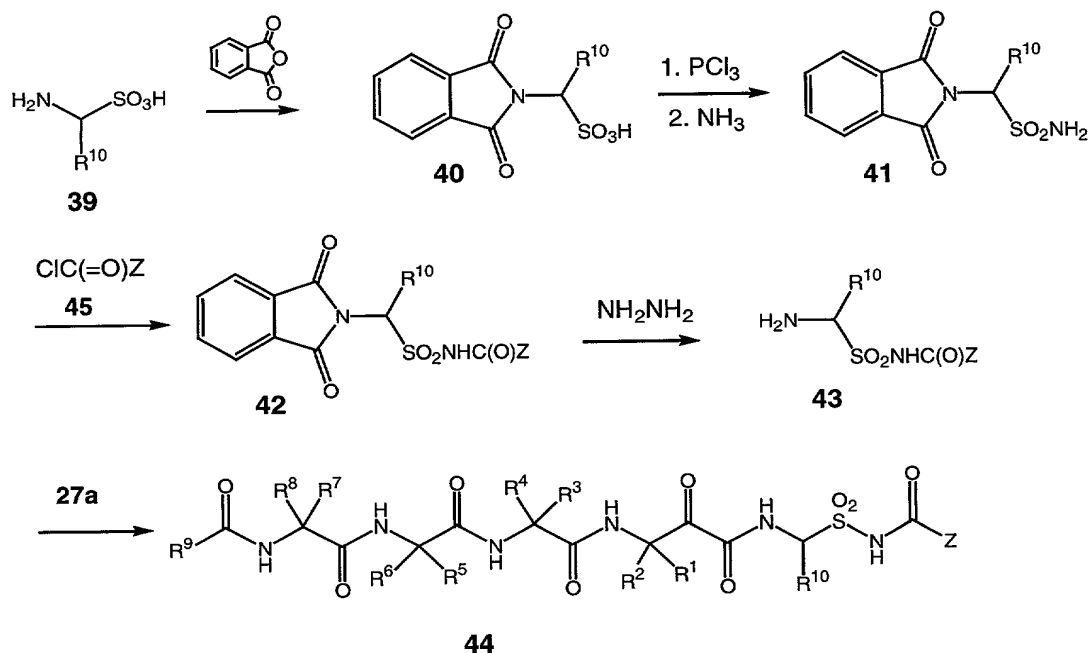
A series of  $\alpha$ -ketoamides of formula **38** are prepared by  
the method outlined in Scheme 7. Treatment of intermediate  
**27b** with sulfonamide of type **39** in the presence of a  
coupling agent such as EDCI and DMAP provides  $\alpha$ -ketoamide  
20 **38**. (Andery, R. H.; J. Org. Chem. 1986, 987).

## Scheme 7



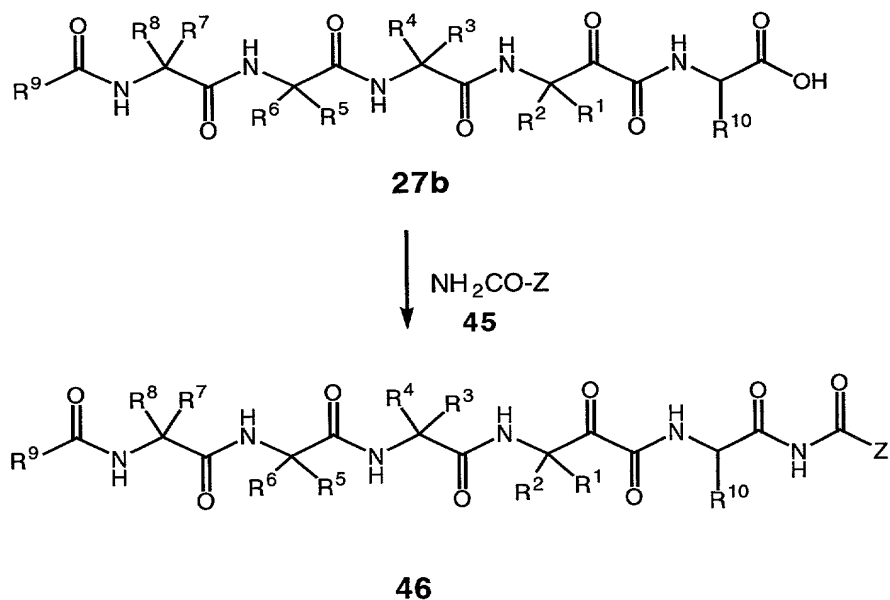
10        A series of  $\alpha$ -ketoamides of formula **44** are prepared by  
the method outlined in Scheme 8. Protection of the amino  
group in **39** gives sulfonic acid **40**. Treatment of compound  
**40** with  $\text{PCl}_3$  followed by ammonia yields sulfonamide **41**.  
Acylation of **41** with an acid chloride of type **45** affords  
15        acyl sulfonamide **42**. Deprotection of the N terminal **42**  
with hydrazine gives amine **43**. Coupling of amine **43** with  
 $\alpha$ -ketoacid **27a** provides  $\alpha$ -ketoamide **44**.

Scheme 8



A series of  $\alpha$ -ketoamides of formula **46** are prepared by the method outlined in Scheme 9. Treatment of intermediate **27b** with amide of type **45** in the presence of DCC and DMAP provides  $\alpha$ -ketoamide **46**. (Almeida, P. S. et al. *Tetrahedron Lett.* **1991**, 23, 2671).

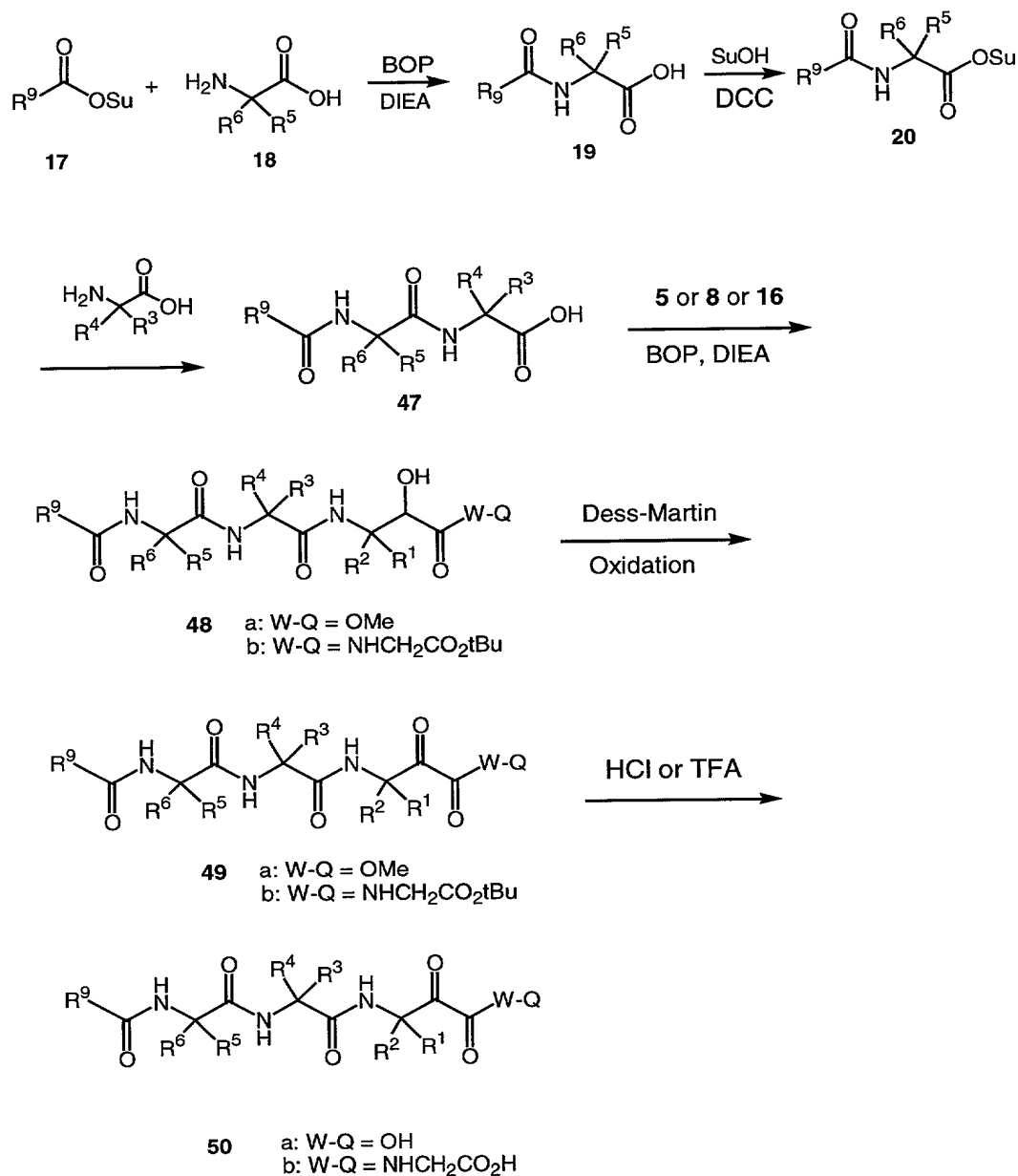
Scheme 9



A series of  $\alpha$ -ketoamides of formula **50** are prepared by a similar method to the preparation of compound **27** as outlined in Scheme 10.

Many of the CBZ protected amino acids and amino acid methyl esters are commercially available or may be prepared from commercial amino acid derivatives by simple protecting group manipulations. Others may be synthesized in racemic form using the Strecker synthesis or amidomalonate synthesis. In addition, the Myers pseudoephedrine glycinamide alkylation method (Myers, A. G.; Gleason, J. L.; Yoon, T; Kung, D. W.. *J. Am. Chem. Soc.* **1997**, *119*, 656-673) and the Evans electrophilic azidation (Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011) may be used to prepare unnatural amino acids in enantiomerically pure form.

## Scheme 10



When required, separation of the racemic material can be achieved by HPLC using a chiral column or by a resolution using a resolving agent such as camphonic chloride as in Steven D. Young, et al, *Antimicrobial Agents and Chemotherapy* **1995**, 2602-2605. A chiral compound of Formula I may also be directly synthesized using a chiral catalyst or a chiral ligand, e.g., Andrew S. Thompson, et al, *Tet. lett.* **1995**, 36, 8937-8940).

5 Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments which are given for illustration of the invention and are not intended to be limiting thereof.

#### Examples

10 Abbreviations used in the examples are defined as follows: "1 x" for once, "2 x" for twice, "3 x" for thrice, "°C" for degrees Celsius, "rt" for room temperature, "eq" for equivalent or equivalents, "g" for gram or grams, "mg" for milligram or milligrams, "mL" for milliliter or  
15 milliliters, "M" for molar, "mmol" for millimole or millimoles, "min" for minute or minutes, "h" for hour or hours, "MS" for mass spectrometry, "NMR" for nuclear magnetic resonance spectroscopy, "<sup>1</sup>H" for proton, "HPLC" for high pressure liquid chromatography, "tlc" for thin  
20 layer chromatography, "v/v" for volume to volume ratio, "atm" for atmosphere, "α", "β", "R", and "S" are stereochemical designations familiar to one skilled in the art.

Abbreviations used in the specification are defined as  
25 follows:

"BOP" is benzotriazol-1-yloxy-tris(dimethylamino)-  
phosphonium hexafluorophosphate;  
"Bzl" or "Bn" is benzyl;  
"CBZ" is carbobenzyloxy;  
30 "COD" is cyclooctadiene;  
"DCC" is 1,3-dicyclohexylcarbodiimide;  
"(DHQ)<sub>2</sub>PHAL" is hydroquinine 1,4-phthalazinediyl  
diether;  
"DIBAL" is diisobutylaluminum hydride;  
35 "DIEA" is Diisopropylethylamine;  
"DMAP" is 4-dimethylamino pyridine;  
"DMF" is dimethylformamide ;  
"DMSO" is dimethylsulfoxide;  
"Duphos" is (+)-1,2-bis(2S,5S)-2,5-  
40 diethylphospholano)-

5 benzene(cyclooctadiene)rhodium(I)  
trifluoromethanesulfonate  
"EtOAc" is ethylacetate;  
"EDCI" is 1-(3-dimethylaminopropyl)-3-  
ethylcarbodiimide hydrochloride;  
10 "Pz" is pyrazinyl;  
"SuOH" is N-hydroxysuccinimide; and  
"TFA" is trifluoroacetic acid.

#### Example A1

15 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-  
L-alanyl-2-oxo-(3 S)-3-amino pentanoylglycine

Step (A1a): At 0°C, DIEA (12.1mL, 69.5 mmol) was added to  
the suspension of Ph<sub>3</sub>PCH<sub>2</sub>CNCl in CH<sub>2</sub>Cl<sub>2</sub>. The suspension  
20 turned to clear. The aminobutyric acid (15.0g, 63.2 mmol)  
was added followed by addition of EDCI (12.7g, 66.4 mmol)  
and DMAP (0.77g, 6.32 mmol). The resulted mixture was  
stirred at 0°C for 2h and at rt over night. Most of the  
solvent was evaporated and the residue was chromatographed  
25 on silica gel (50-60% EtOAc:Hexane). The product (Scheme  
1, 2) was obtained as a white solid 22.7g in 69% yield. MS  
found (M+1)<sup>+</sup> 521.3

Step (A1b): The ylide obtained from Step(A1a) (10g, 19.2  
30 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (200 mL) and the mixture was  
cooled to -78°C. To this mixture at -78°C was purged O<sub>3</sub>  
until the color changed to blue. Excess O<sub>3</sub> was removed by  
purging N<sub>2</sub> into the mixture. The solution of Gly-OtBu  
hydrochloride (3.54g, 21.1 mmol), pretreated with DIEA and  
35 precooled) in CH<sub>2</sub>Cl<sub>2</sub> was added at -78°C to the above  
reaction mixture and stirred at -78°C for 30 min, then  
warmed to rt. Solvent was evaporated and the residue was  
chromatographed on silica gel (20-50% EtOAc:hexane). The  
α-ketoamide (Scheme 1, 3) was obtained in 58% yield as an  
40 oil (4.25g). MS found (M+Na)<sup>+</sup> 401.1. Similarly, the

5 reaction mixture can be quenched with methanol instead of Gly-OtBu to provide the corresponding  $\alpha$ -ketoester (Scheme 1, **3a**).

Step (A1c): To a solution of ketoamide obtained from Step  
10 (A1b) (0.23g, 0.61 mmol) in THF (10 mL) at 0°C was added sodium borohydride (42mg, 1.22mmol) in portions. After stirring at 0°C for 30 min, the reaction mixture was quenched with acetone. Most of the solvent was evaporated and the residue was dissolved in EtOAc, washed with H<sub>2</sub>O and  
15 brine. Chromatography on silica gel (40% EtOAc in hexane) yielded 124 mg  $\alpha$ -hydroxyamide (Scheme 1, **4**) as a colorless oil (53%). MS found (M+1)<sup>+</sup> 381.2.

Step (A1d): The  $\alpha$ -hydroxyamide obtained from Step (A1c)  
20 (124 mg, 0.326 mmol) was dissolved in MeOH (50 mL) and Pd/C (10mg) was added. The mixture was hydrogenated under 1 atm. for 40 min. The reaction mixture was filtered and concentrated. The amine (Scheme 1, **5**) was obtained in 99% yield as a white solid 82 mg. MS found (M+1)<sup>+</sup> 247.3.  
25 Similarly, the  $\alpha$ -ketoester from (A1b) was converted to  $\alpha$ -hydroxyester (Scheme 1, **5a**) via step (A1c).

Step (A1e): DCC (3.99g, 19.3 mmol, 1.2 eq) was added to a solution of 2-pyrazine carboxylic acid (2.0g, 16.1 mmol)  
30 and N-hydroxysuccinimide (1.95g, 16.9 mmol, 1.05eq) in 100mL THF at 0°C. The mixture was stirred at rt over night. The reaction mixture was filtered, concentrated and dried. The product was obtained in 91% yield as a solid (Scheme 4, **17**).

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Step (A1f): At 0°C under N<sub>2</sub>, DIEA (13.3mL, 76.13 mmol) was added to a solution of material from Step (A1e) (10g, 45.2 mmol) and leucine (5.93g, 45.3 mmol) in 120 mL DMF. After addition, the resulted mixture was stirred at rt over  
40 night. The mixture was diluted with 200 mL of EtOAc,



5 washed with 1N HCl (2x30 mL), H<sub>2</sub>O (2x50 mL) and brine, and dried over MgSO<sub>4</sub>. The solvent was removed and dried on vacuum to provide a white solid as pure product (95%) (Scheme 4, **19**). MS found (M-1)<sup>-</sup> 219.

10 Step (A1g): Following a procedure analogous to Step (A1e), the material from Step (A1f) (1.0g, 4.5 mmol) was treated with N-hydroxysuccinimide (530 mg, 4.5 mmol), providing the desired product as a white solid (1.28g, 90%) (Scheme 4, **20**).

15

Step (A1h): Following a procedure analogous to Step (A1f), the succinimide ester of N-Boc isoleucine (10g, 30.45 mmol) was treated with cyclohexylalanine (6.32g, 30.45 mmol) in the presence of DIEA in DMF, providing the desired product (Scheme 4, **23**) as a white solid (95%). MS found (M+1)<sup>+</sup> 385.3.

20

Step (A1i): The material from Step (A1h) (1.0g, 2.6 mmol) was treated with 4M HCl in dioxane for 2h at rt. Solvent was evaporated and the residue was dried. Following a procedure analogous to Step (A1f), the material from above was treated with the material from Step (A1g) (0.83g, 2.6 mmol) in the presence of DIEA in DMF, providing the desired product (Scheme 4, **24**) as a white solid (1.16g, 89%). MS found (M+1)<sup>+</sup> 504.3.

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Step (A1j): To a solution of the above material from Step (A1i) (1g, 1.99 mmol) in 100mL of DMF at 0°C was added BOP (1.3g, 2.98 mmol) and DIEA (0.52 mL, 2.98 mmol). The mixture was stirred at this temp. for 20 min. Then a solution of the material from Step (A1d) (490 mg, 1.99 mmol) in 10 mL of DMF was added to the above mixture followed by addition of another portion of DIEA (0.52 mL, 1.99 mmol). The resulting mixture was stirred at 0°C for 1h and rt overnight. The reaction mixture was diluted with EtOAc (400 mL), washed with 1N HCl, saturated NaHCO<sub>3</sub>, H<sub>2</sub>O,

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- 5 brine, dried and concentrated. Chromatography on silica gel (70% EtOAc in hexane) provided desired product (1.22g, 84%) as a white solid (Scheme 4, **25b**). MS found (M+1)<sup>+</sup> 732.4.
- 10 Step (A1k): To a mixture of the above material from Step (A1j) (200 mg, 0.27 mmol) and molecular sieves in 6 mL of CH<sub>2</sub>Cl<sub>2</sub> was added Dess-Martin reagent (172 mg, 0.41 mmol). The resulting mixture was stirred at rt for 2h. Then the mixture was filtered and the residue was chromatographed on
- 15 silica gel (5% MeOH in CHCl<sub>3</sub>) to provide the desired ketoamide (Scheme 4, **26b**) as a white solid (169mg, 86%). MS found (M+1)<sup>+</sup> 730.3.
- Step (A1l): A solution of the above material from Step
- 20 (A1k) (300 mg, 0.41 mmol) in CH<sub>2</sub>Cl<sub>2</sub> was treated with TFA (20 mL, 1:1) and the mixture was stirred at rt for 2h. After evaporation of the solvent, the residue was dried in vacuum and the title ketoamide (Scheme 4, **27b**), Example 1A, was obtained (273 mg, 99%) as a light yellow solid. MS
- 25 found (M+1)<sup>+</sup> 674.4.

#### Example A2

(3S)-2-oxo-3-{[N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl]amino}-N-(2H-tetrazol-5-ylmethyl) pentanamide

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Step (A2a): The ylide obtained from Step (A1a) (10g, 19.2 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (200 mL) and the mixture was cooled to -78°C. To this mixture was purged O<sub>3</sub> at this

35 temp. until the color of the mixture changed to blue. Excess O<sub>3</sub> was removed by purging N<sub>2</sub> into the mixture. Methanol was added at -78°C to the above reaction mixture. The resulting mixture was stirred at -78°C for 30 min and warmed to rt. Solvent was evaporated and the residue was

40 chromatographed on silica gel (20-50% EtOAc:hexane). The

5  $\alpha$ -ketoester (Scheme 1, **3a**) was obtained in 87% yield as a white solid. MS found (M+Na)<sup>+</sup> 280.4.

Step (A2b): Following a procedure analogous to Step (A1c), the ketoester from Step (A2a) (1g, 3.6 mmol) was reduced  
10 with NaBH<sub>4</sub> to the desired  $\alpha$ -hydroxyester (Scheme 1, **4a**) as a white solid (0.86g, 86%). MS found (M+1)<sup>+</sup> 282.3.

Step (A2c): Following a procedure analogous to Step (A1d), the  $\alpha$ -hydroxyester (0.7g, 2.5 mmol) from Step (A2b) above  
15 was hydrogenated in the present of 10% Pd/C to give the desired amine (Scheme 1, **5a**) as a white solid (3.6g, >95%). MS found (M+1)<sup>+</sup> 148.3.

Step (A2d): Following a procedure analogous to Step (A1j),  
20 the material from Step (A2c) above (0.5g, 3.4 mmol) was coupled with the material from Step (A1i) (1.7g, 3.4 mmol) to provide the desired the  $\alpha$ -hydroxyester (Scheme 4, **25a**) as a white solid (1.4g, 67%). MS found (M+1)<sup>+</sup> 633.3.

25 Step (A2e): To a solution of the above material from Step (A2d) (500 mg, 0.79 mmol) in 8 mL THF at 0°C was added 8mL of 1N LiOH solution. After stirring at this temp for 3h, the mixture was acidified with 1N HCl to pH 5. Solvent was evaporated and the residue was extrated with EtOAc (3x50  
30 mL). The combined organic portion was washed with water, brine and dried. Removal of solvent yielded the acid product (463mg, 95%) as white solid. MS found (M+1)<sup>+</sup> 619.2, (M-1)<sup>-</sup> 617.1.

35 Step (A2f): Aminomethyltetrazole (75 mg, 0.76 mmol) was suspended in 6 mL mixed solvent of DMF/DMSO (1:1). To this mixture was added DIEA (0.3 mL), material from Step (A2e) above (50 mg, 0.081 mmol) and BOP reagent (200 mg). The resulting mixture was stirred at rt for 3h. Then the  
40 mixture was HPLC purified (grandient starting from 30%

5 water in acetonitrile) to give the desired product as a white solid (46mg, 82%). MS found (M+1)<sup>+</sup> 701.4.

Step (A2g): The material from Step (A2f) above (46 mg, 0.066 mmol) was dissolved in 5.0 mL methylenechloride. 10 Dess-Martin reagent (100 mg) was added. The mixture was stirred at rt for 1.5h. Then the reaction mixture was filtered and solvent was removed. HPLC purification (gradient starting from 30% water in acetonitrile) gave Example A2, a white solid, as pure product (40mg, 89%). MS 15 found (M+1)<sup>+</sup> 698.4.

#### Example A3

2-oxo-3-[[N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl]amino]-N-(sulfomethyl)pentanamide

20 Step (A3a): Following a procedure analogous to Step (A2f), the material from Step (A2e) (50 mg, 0.081 mmol) was coupled with aminomethanesulfonic acid (18 mg, 0.16 mmol), providing the title product as a light-yellow solid (44mg, 25 76%). MS found (M+1)<sup>+</sup> 712.3.

Step (A3b): Following a procedure analogous to Step (A2g), the above material from Step (3a) (44mg, 0.062 mmol) was oxidized with Dess-Martin reagent to give the title α- 30 ketoamide (30mg, 68%). MS found (M+1)<sup>+</sup> 710.3.

#### Example A4

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(2-nitrophenyl)sulfonyl]glycinamide 35

Step (A4a): To the mixture of the material from Step (A11) (Scheme 4, **27b**) (34 mg, 0.05 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5mL) at 0°C were added a solution of (2-nitrophenyl)sulfonamide (15 mg, 40 0.075 mmol) and DMAP (6mg, 0.05mmol) in CH<sub>2</sub>Cl<sub>2</sub>, followed by addition of EDCI (14.3 mg, 0.075 mmol). The resulting

5 mixture was stirred at rt for 40 min. The reaction mixture was diluted with EtOAc, washed with H<sub>2</sub>O, brine, dried and concentrated. HPLC purification gave the title product as a white solid. MS found (M+1)<sup>+</sup> 858.3.

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**Example A5**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-(methylsulfonyl)glycinamide

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Step (A5a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with methylsulfonamide to provide the title compound. MS found (M+1)<sup>+</sup> 751.4.

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**Example A6**

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N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(phenylmethyl)sulfonyl]glycinamide

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Step (A6a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with phenylmethylsulfonamide to provide the title compound. MS found (M+1)<sup>+</sup> 825.4.

**Example A7**

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N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-(phenylsulfonyl)glycinamide

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Step (A7a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with phenylsulfonamide to provide the title compound. MS found (M+1)<sup>+</sup> 813.4.

**Example A8**

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N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(trifluoromethyl)sulfonyl]glycinamide

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Step (A8a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with trifluoromethylsulfonamide to provide the title compound. MS found (M+1)<sup>+</sup> 805.4.

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**Example A9**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(2-nitrophenyl)sulfonyl]glycinamide

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Step (A9a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with (2-nitrophenyl)sulfonamide to provide the title compound. MS found (M+1)<sup>+</sup> 858.1.

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**Example A10**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(4-nitrophenyl)sulfonyl]glycinamide

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Step (A10a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with (4-nitrophenyl)sulfonamide to provide the title compound. MS found (M+1)<sup>+</sup> 858.3.

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**Example A11**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(4-fluorophenyl)sulfonyl]glycinamide

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Step (A11a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with (4-fluorophenyl)sulfonamide to provide the title compound. MS found (M+1)<sup>+</sup> 831.4.

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**Example A12**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3 S)-3-amino pentanoyl-N-[(3-fluorophenyl)sulfonyl]glycinamide

10 Step (A12a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with (3-fluorophenyl)sulfonamide to provide the title compound. MS found (M+1)<sup>+</sup> 831.4.

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**Example A13**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(2-fluorophenyl) sulfonyl]glycinamide

20 Step (A13a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with (2-fluorophenyl)sulfonamide to provide the title compound. MS found (M+1)<sup>+</sup> 831.5.

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**Example A14**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(4-chlorophenyl) sulfonyl]glycinamide

30 Step (A14a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with (4-chlorophenyl)sulfonamide to provide the title compound. MS found (M+1)<sup>+</sup> 848.3.

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**Example A15**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentano yl-N-[(3-chlorophenyl) sulfonyl]glycinamide

40 Step (A15a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with (3-

5 chlorophenyl)sulfonamide to provide the title compound. MS  
found (M+1)<sup>+</sup> 848.4.

**Example A16**

10 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-  
cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[[4-  
(thionitroso) phenyl]sulfonyl]glycinamide

Step (A16a) Following a procedure analogous to Step (A4a),  
compound **27b** (Scheme 4) was coupled with 4-  
15 (thionitroso)phenylsulfonamide to provide the title  
compound. MS found (M+1)<sup>+</sup> 870.6.

**Example A17**

20 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-  
cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[[4-  
[(trifluoromethyl)sulfonyl]phenyl]sulfonyl]glycinamide

Step (A17a) Following a procedure analogous to Step (A4a),  
compound **27b** (Scheme 4) was coupled with 4-  
25 [(trifluoromethyl)sulfonyl]phenyl-sulfonamide to provide  
the title compound. MS found (M+1)<sup>+</sup> 946.1.

**Example A18**

30 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-  
cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[[4-  
(trifluoromethyl)phenyl]sulfonyl]glycinamide

Step (A18a) Following a procedure analogous to (4a),  
compound **27b** (Scheme 4) was coupled with 4-  
35 (trifluoromethyl)-phenylsulfonamide to provide the title  
compound. MS found (M+1)<sup>+</sup> 881.8.

**Example A19**

40 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-  
cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(4-  
cyanophenyl)sulfonyl]glycinamide



5

Step (A19a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 4-cyanophenylsulfonamide to provide the title compound. MS found (M+1)<sup>+</sup> 839.0.

10

**Example A20**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(3-chloro-4-methylphenyl)sulfonyl]glycinamide

15

Step (A20a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 3-chloro-4-methylphenylsulfonamide to provide the title compound. MS found (M+1)<sup>+</sup> 862.3.

20

**Example A21**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(4-chloro-3-nitrophenyl)sulfonyl]glycinamide

25

Step (A21a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 4-chloro-3-nitrophenylsulfonamide to provide the title compound. MS found (M+1)<sup>+</sup> 893.4.

30

**Example A22**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(3,5-dichlorophenyl)sulfonyl]glycinamide

35

Step (A22a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 3,5-dichlorophenylsulfonamide to provide the title compound. MS found (M+1)<sup>+</sup> 882.9.

40

5

**Example A23**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(4-methyl-3-nitrophenyl)sulfonyl]glycinamide

10 Step (A23a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 4-methyl-3-nitrophenylsulfonamide to provide the title compound. MS found (M+1)<sup>+</sup> 873.1.

15

**Example A24**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[[2-chloro-5-(trifluoromethyl)phenyl]sulfonyl]glycinamide

20 Step (A24a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 2-chloro-5-(trifluoromethyl)phenyl-sulfonamide to provide the title compound. MS found (M+1)<sup>+</sup> 916.5.

25

**Example A25**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(5-carboxy-2-chlorophenyl)sulfonyl]glycinamide

30 Step (A25a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 5-carboxy-2-chlorophenylsulfonamide to provide the title compound. MS found (M+1)<sup>+</sup> 892.3.

35

**Example A26**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(2,5-dichlorophenyl)sulfonyl]glycinamide

40 Step (A26a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 2,5-

5 dichlorophenylsulfonamide to provide the title compound. MS  
found (M+1)<sup>+</sup> 879.5.

**Example A27**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-  
10 cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(3,4-  
difluorophenyl)sulfonyl]glycinamide

Step (A27a) Following a procedure analogous to Step (A4a),  
compound **27b** (Scheme 4) was coupled with 3,4-  
15 difluorophenylsulfonamide to provide the title compound. MS  
found (M+1)<sup>+</sup> 849.6.

**Example A28**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-  
20 cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(3,5-dichloro-  
2-hydroxyphenyl)sulfonyl]glycinamide

Step (A28a) Following a procedure analogous to Step (A4a),  
compound 27b (Scheme 4) was coupled with 3,5-dichloro-2-  
25 hydroxyphenylsulfonamide to provide the title compound. MS  
found (M-1)<sup>-</sup> 895.5.

**Example A29**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-  
30 L-alanyl-2-oxo-(3S)-3-amino pentanoyl-N-[(2,4,5-  
trichlorophenyl)-sulfonyl]glycinamide

Step (A29a) Following a procedure analogous to Step (A4a),  
compound **27b** (Scheme 4) was coupled with 2,4,5-  
35 trichlorophenylsulfonamide to provide the title compound.  
MS found (M-1)<sup>-</sup> 913.3.

**Example A30**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-  
40 cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(5-carboxy-4-  
chloro-2-fluorophenyl)sulfonyl]glycinamide

5

Step (A30a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 5-carboxy-4-chloro-2-fluorophenyl sulfonamide to provide the title compound. MS found (M+1)<sup>+</sup> 910.6.

10

**Example A31**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[[5-(dimethylamino)-1-naphthalenyl]sulfonyl]glycinamide

15

Step (A31a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 5-(dimethylamino)-1-naphthalenylsulfonamide to provide the title compound. MS found (M+1)<sup>+</sup> 907.3.

20

**Example A32**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-(2-naphthalenylsulfonyl)glycinamide

25

Step (A32a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 2-naphthalenylsulfonamide to provide the title compound. MS found (M+1)<sup>+</sup> 864.2.

30

**Example A33**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[(4-(phenyl)phenyl)-sulfonyl]glycinamide

35

Step (A33a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 4-biphenylsulfonamide to provide the title compound. MS found (M+1)<sup>+</sup> 889.5.

40

5

**Example A34**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(6-ethoxy-2-benzothiazolyl)sulfonyl]glycinamide

- 10 Step (A34a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with (6-ethoxy-2-benzothiazolyl)sulfonamide to provide the title compound. MS found (M+1)<sup>+</sup> 915.2.

15

**Example A35**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[[2-chloro-5-[(phenylmethyl)amino]carbonyl]phenyl]sulfonyl]glycinamide

- 20 Step (A35a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 2-chloro-5-[[[(phenylmethyl)amino]carbonyl]-phenyl sulfonamide to provide the title compound. MS found (M+1)<sup>+</sup> 980.6.

25

**Example A36**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[2-chloro-5-[(2-trifluoroethyl)amino]carbonyl]phenyl]sulfonyl]glycinamide

- 30 Step (A36a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with [[(2-trifluoroethyl)amino]carbonyl]phenyl sulfonamide to provide the title compound. MS found (M-1)<sup>-</sup> 970.5.

35

**Example A37**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[2-chloro-5-[(cyclopropylmethyl)amino]carbonyl]phenyl]sulfonyl]glycinamide

40

5 Step (A37a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 2-chloro-5-[[cyclopropylmethyl]amino]-carbonyl]phenyl] sulfonamide to provide the title compound. MS found (M+1)<sup>+</sup> 944.4.

10

**Example A38**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[3-nitro-4-(2-pyrimidinylthio)phenyl]sulfonyl]glycinamide

15

Step (A38a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 3-nitro-4-(2-pyrimidinylthio)phenyl sulfonamide to provide the title compound. MS found (M+1)<sup>+</sup> 968.4.

20

**Example A39**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[2-chloro-4-(acetylamino)phenyl]sulfonyl]glycinamide

25

Step (A39a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 2-chloro-4-(acetylamino)phenyl sulfonamide to provide the title compound. MS found (M-1)<sup>-</sup> 902.5.

30

**Example A40**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[3-chloro-4-(2-benzoxazolylthio)phenyl]sulfonyl]glycinamide

35

Step (A40a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 3-chloro-4-(2-benzoxazolylthio)phenyl sulfonamide to provide the title compound. MS found (M-1)<sup>-</sup> 1005.5.

5

**Example A41**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3 S)-3-amino pentanoyl-N-[[3,5-dichloro-4-(4-nitrophenoxy)phenyl]sulfonyl]glycinamide

- 10 Step (A41a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 3,5-dichloro-4-(4-nitrophenoxy)phenyl sulfonamide to provide the title compound. MS found (M+1)<sup>+</sup> 1018.5.

15

**Example A42**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3 S)-3-amino pentanoyl-N-[[5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl]glycinamide

- 20 Step (A42a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 5-(acetylamino)-1,3,4-thiadiazol-2-yl sulfonamide to provide the title compound. MS found (M+1)<sup>+</sup> 878.5.

25

**Example A43**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3 S)-3-amino pentanoyl-N-[(3-cyanophenyl)sulfonyl]glycinamide

- 30 Step (A43a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 3-cyanophenylsulfonamide to provide the title compound. MS found (M+1)<sup>+</sup> 838.4.

35

**Example A44**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3 S)-3-amino pentanoyl-N-[(3-(aminosulfonyl)-5-chlorophenyl)sulfonyl]glycinamide

- 40 Step (A44a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 3-(aminosulfonyl)-

5 5-chlorophenyl sulfonamide to provide the title compound.  
MS found (M-1)<sup>-</sup> 924.4.

**Example A45**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-  
10 L-alanyl-2-oxo-(3S)-3-amino pentanoyl-N-[[3,5-  
bis(trifluoromethyl)phenyl]sulfonyl]glycinamide

Step (A45a) Following a procedure analogous to Step (A4a),  
compound **27b** (Scheme 4) was coupled with 3,5-  
15 bis(trifluoromethyl)phenyl sulfonamide to provide the title  
compound. MS found (M+1)<sup>+</sup> 949.4.

**Example A46**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-  
20 L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[4-[5-[3-(4-  
chlorophenyl)-3-oxo-1-propenyl]-2-  
furanyl]phenyl]sulfonyl]glycinamide

Step (A46a): Following a procedure analogous to step (A4a),  
25 compound **27b** (Scheme 4) was coupled with 4-[5-[3-(4-  
chlorophenyl)-3-oxo-1-propenyl]-2-furanyl]phenyl  
sulfonamide providing the title compound. MS found (M+1)<sup>+</sup>  
1043.5.

**Example A47**

30 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-  
L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[3-  
[(phenylmethyl)amino]carbonyl]phenyl]sulfonyl]glycinamide

35 Step (A47a): Following a procedure analogous to step (A4a),  
**27b** (Scheme 4) was coupled with 3-[(phenylmethyl)amino]-  
carbonyl]phenyl]sulfonamide providing the title product as  
crystalline solid. MS found (M+1)<sup>+</sup> 946.6.



5

**Example A48**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[3-[(2,2,2-trifluoroethyl)amino]carbonyl]phenyl]sulfonyl]glycinamide

10 Step (A48a): Following a procedure analogous to step (A4a), **27b** (Scheme 4) was coupled with 3-[(2,2,2-trifluoroethyl)amino]carbonyl]phenyl]sulfonamide providing the title product as crystalline solid. MS found (M+1)<sup>+</sup> 938.5.

15

**Example A49**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[3-[(benzoylamino)sulfonyl]-5-chlorophenyl]sulfonyl]glycinamide

20

Step (A49a): Following a procedure analogous to step (A4a), **27b** (Scheme 4) was coupled with 3-[(benzoylamino)sulfonyl]-5-chlorophenyl]-sulfonamide providing the title product as crystalline solid. MS found (M+1)<sup>+</sup> 1030.6.

25

**Example A50**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoylglycine

30

Step (A50a): To a suspension of KOtBu (3.55g, 31.7mmol) in 15mL CH<sub>2</sub>Cl<sub>2</sub> was added N-CBZ-phosphonolycine trimethyl ester (9.46g, 28.5mmol) at -78°C under N<sub>2</sub>. This mixture was stirred for 15min at this temperature and 2,2-difluoroacetaldehyde ethyl hemiacetal (4.0g, 31.7mmol) was added slowly. The resulted mixture was warmed up to room temperature and stirred overnight. Most solvent was removed and the residue was dissolved in ethyl acetate. The mixture was washed with cold water, dried over magnesium sulfate and concentrated. Flash chromatography (10-15% EtOAc/Hexane) gave the desired alkene (1.97g, 24%) (Scheme

40

5 3, **11**) as a clear oil (4:1 mixture of Z:E isomers).  
(M+1)<sup>+</sup> 286.3.

Step (A50b): A mixture the material from Step (A50a)  
(0.90g, 3.16mmol) and of (+)-1,2-bis((2S,5S)-2,5-diethyl-  
10 phospholano)benzene-(cyclooctadiene)rhodium(I)  
trifluoromethanesulfonate ([Rh(COD)(S,S-di-Ethyl-  
DUPHOS)]<sup>+</sup>CF<sub>3</sub>SO<sub>3</sub><sup>-</sup>) (25mg, 0.03mmol, 1 mol%) in 20mL MeOH  
was hydrogenated at 50psi for 15h. After evaporation of  
solvent, the residue was dissolved in 30% EtOAc/Hexane and  
15 the solution was passed through a pad of silica gel to  
remove trace amount of the catalyst. Evaporation of  
solvent yielded the desired compound (Scheme 3, **12**) as a  
crystalline solid (0.91g, 100%).

20 Step (A50c): To a solution of the material from Step  
(A50b) (1.95g, 5.23mmol) in 50mL CH<sub>2</sub>Cl<sub>2</sub> under N<sub>2</sub> was added  
dropwise 5.49mL DIBAL (1.0M solution in CH<sub>2</sub>Cl<sub>2</sub>, 5.49mmol)  
at -78°C over 15min. After stirring at this temperature  
for 2h, the mixture was quenched with 10mL 5% potassium  
25 hydrogen sulfate solution. Then the mixture was warmed up  
to room temperature, diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed with  
KHSO<sub>4</sub>, NaHCO<sub>3</sub> and brine, dried over NaSO<sub>4</sub> and concentrated.  
Flash chromatography (15-30% EtOAc/Hexane) afforded 1.20g  
(89%) of the desired aldehyde (Scheme 3, **13**) as a white  
30 solid.

Step (A50d): Butyl lithium (2.5M solution in hexane, 4.1mL,  
10.3mmol) was added dropwise to a solution of  
tris(methylthio)methane (1.58g, 10.3mmol) in 20mL THF at  
35 -64°C and the mixture was stirred at this temperature for  
20min. Then a solution of 0.66g (2.57mmol) of the  
material from Step (A50c) in 5.0mL THF was added dropwise to  
the above mixture over 10min. The resulting mixture was  
stirred at -30°C and warmed up to room temperature. Then  
40 the reaction mixture was quenched with saturated NH<sub>4</sub>Cl, and  
diluted with ethyl acetate. The organic phase was

5 separated and washed with 5% KHSO<sub>4</sub>, H<sub>2</sub>O, NaHCO<sub>3</sub>, brine,  
dried over NaSO<sub>4</sub> and concentrated. Flash chromatography  
(10-15% EtOAc/Hexane) yielded 0.90g (85%) of the desired  
product (Scheme 3, **14**) as a clear oil (a mixture of two  
diastereomers).

10 Step (A50e): To a solution of 0.15g (0.36mmol) of the  
material from Step (A50d) in a mixed solvent of MeOH/H<sub>2</sub>O  
(12mL/1.0mL) were added 0.46g (1.69mmol) mercury(II)  
chloride and 0.12g (0.58mmol) mercury(II) oxide. The  
15 resulted suspension was stirred at room temperature for 2h.  
Then the reaction mixture was filtered through a pad of  
Celite and most of the solvent was removed. The residue  
was dissolved in ethyl acetate, and this mixture was washed  
20 with 70% ammonium acetate, saturated ammonium chloride,  
sodium bicarbonate and dilute NaCl solution, dried over  
magnesium sulfate and concentrated. Chromatography (30%  
EtOAc/Hexane) gave 0.11g (96%) of the desired product  
(Scheme 3, **15**) as a clear oil (a mixture of two  
diastereomers).

25 Step (A50f): Following a procedure analogous to Step  
(A1d), the material from Step (A50e) was hydrogenated to  
afford the desired  $\alpha$ -hydroxyl  $\beta$ -amino ester (Scheme 3, **16**)  
as a crystalline solid.

30 Step (A50g): Following a procedure analogous to Step (A1j),  
the material from Step (A50f) was coupled with compound **24**  
(Scheme 4) to give the  $\alpha$ -hydroxyester (Scheme 4, **25a**) as a  
crystalline solid.

35 Step (A50h): Following a procedure analogous to Step  
(A2e), the material from Step (A50g) was converted to the  
desired  $\alpha$ -hydroxyacid.

40 Step (A50i): Following a procedure analogous to Step  
(A1i), the above acid from Step (A50h) was coupled with

5 Gly-OtBu to afford the desired product (Scheme 4, **25b**) as a crystalline solid.

Step (A50j): Following a procedure analogous to Step (A1k), the material from Step (A50i) was oxidized to  $\alpha$ -  
10 ketoamide (Scheme 4, **26b**) as crystalline solid.

Step (A50k): Following a procedure analogous to Step (A1l), the material from Step (A50j) was treated with TFA to afford the title compound (Scheme 4, **27b**) as a white  
15 solid. MS found (M+1)<sup>+</sup> 710.4.

#### Example A51

(3S)-5,5-difluoro-2-oxo-3-[[N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl]amino]-N-(2H-tetrazol-5-ylmethyl)pentanamide  
20

Step (A51a): Following a procedure analogous to Steps (A1f) and (A1g), the material from Step (A50h) was coupled with aminomethyltetrazole to afford the title product as  
25 acrySTALLINE solid. MS found (M+1)<sup>+</sup> 734.4.

#### Example A52

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[(3,5-dichlorophenyl)sulfonyl]glycinamide  
30

Step (A52a) Following a procedure analogous to Step (A4a), the material from Step (A50k) was coupled with 3,5-dichlorophenyl-sulfonamide to give the title product. MS  
35 found (M+1)<sup>+</sup> 918.9.

#### Example A53

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[(3-chlorophenyl)sulfonyl]glycinamide  
40

5 Step (A53a) Following a procedure analogous to Step (A4a),  
the material from Step (A50k) was coupled with 2-  
chlorophenylsulfonamide to give the title product. MS found  
(M+1)<sup>+</sup> 883.3.

10

**Example A54**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-  
L-alanyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[5-  
(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl]-glycinamide

15

Following a procedure analogous to Step (A4a), the material  
from Step (A50k) was coupled with [5-(acetylamino)-1,3,4-  
thiadiazol-2-yl]sulfonamide to give the title product. MS  
found (M+1)<sup>+</sup> 914.5.

20

**Example A55**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-  
L-alanyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-(3-  
aminosulfonyl-5-chlorophenyl)sulfonyl]glycinamide

25

Step (A55a): Following a procedure analogous to step (A4a),  
the material from step (A50k) was coupled with [3-  
aminosulfonyl-5-chlorophenyl]sulfonamide to give the title  
product. MS found (M+1)<sup>+</sup> 962.4.

30

**Example A56**

(3S)-5,5,5-trifluoro-2-oxo-3-[[N-(2-pyrazinylcarbonyl)-L-  
leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl]amino]-N-(2H-  
tetrazol-5-ylmethyl)pentanamide

35

Step (A56a): Following a procedure analogous to Steps (A1a-  
d), 2-hydroxyl-3-amino-5-trifluorovaleric acid methylester  
(Scheme1, **5** where R1=H, R2=CH<sub>2</sub>CF<sub>3</sub>, W''=OMe) was obtained.

40

(A56b): Following a procedure analogous to Step (A1j), the  
product from (A56a) was coupled with the product from (A1I)  
to give the desired product (Scheme 4, **25a**).

5 (A56c): Following a procedure analogous to Steps (A2e-g),  
the material from Step (A56b) was converted to the desired  
product as a white solid (Scheme 6). MS found: (M+1)+  
752.9.

10 **Example A57**

*N*-[4-*sec*-butyl-15-{{(3-chloro-5-{{(3,3,3-  
trifluoropropanoyl)amino}sulfonyl}phenyl)sulfonyl}amino}-7-  
(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-  
2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-  
15 pyrazinecarboxamide

Step (A57a): Following a procedure analogous to step (A4a),  
the material from step (A50k) was coupled with (3-chloro-5-  
{{(3,3,3-trifluoropropanoyl)amino}sulfonamide to give the  
20 title product. MS found (M+1)+ 1073.4.

**Example A58**

*N*-[4-*sec*-butyl-15-[(3-chloro-5-  
[(hexanoylamino)sulfonyl]phenyl)sulfonyl]amino]-7-  
25 (cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-  
2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-  
pyrazinecarboxamide

Step (A58a): Following a procedure analogous to step (A4a),  
30 the material from step (A50k) was coupled with (3-chloro-  
5-[(hexanoylamino)sulfonamide to give the title product. MS  
found (M+1)+ 1061.3.

**Example A59**

35 *N*-[15-[[1,1'-biphenyl]-3-ylsulfonyl]amino]-4-*sec*-butyl-7-  
(cyclohexylmethyl)-10-ethyl-1-isobutyl-2,5,8,11,12,15-  
hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-  
pyrazinecarboxamide

40 Step (A59a): Following a procedure analogous to step (A4a),  
the material from step (A50k) was coupled with ([1,1'-

5 biphenyl]-3-yl] sulfonamide to give the title product. MS  
found (M+1)<sup>+</sup> 890.4.

**Example A60**

10 *N*-(4-*sec*-butyl-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-15-  
{[(4'-methoxy[1,1'-biphenyl]-4-yl)sulfonyl]amino}-  
2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl)-2-  
pyrazinecarboxamide

15 Step (A60a): Following a procedure analogous to step (A4a),  
the material from step (A50k) was coupled with [(4'-  
methoxy[1,1'-biphenyl]-4-yl sulfonamide to give the title  
product. MS found (M+1)<sup>+</sup> 920.1.

**Example A61**

20 *N*-(4-*sec*-butyl-7-(cyclohexylmethyl)-15-[(3',5'-  
dichloro[1,1'-biphenyl]-4-yl)sulfonyl]amino)-10-ethyl-1-  
isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-  
1-yl)-2-pyrazinecarboxamide

25 Step (A61a): Following a procedure analogous to step (A4a),  
the material from step (A50k) was coupled with [(3',5'-  
dichloro[1,1'-biphenyl]-4-yl)sulfonamide to give the title  
product. MS found (M+1)<sup>+</sup> 958.5.

**Example A62**

30 *N*-[4-*sec*-butyl-15-[(4'-chloro[1,1'-biphenyl]-3-  
yl)sulfonyl]amino]-7-(cyclohexylmethyl)-10-(2,2-  
difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-  
tetraazapentadec-1-yl]-2-pyrazinecarboxamide

35 Step (A62a): Following a procedure analogous to step (A4a),  
the material from step (A50k) was coupled with [(4'-  
chloro[1,1'-biphenyl]-3-yl)sulfonamide to give the title  
product. MS found (M+1)<sup>+</sup> 960.6.

5

**Example A63**

*N*-[4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-15-({[3-(2-methylphenoxy)phenyl]sulfonyl}amino)-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

10

Step (A63a): Following a procedure analogous to step (A4a), the material from step (A50k) was coupled with [3-(2-methylphenoxy)phenyl]sulfonamide to give the title product. MS found (M+1)<sup>+</sup> 956.2.

15

**Example A64**

*N*-[4-*sec*-butyl-15-({[3-(2-chlorophenoxy)phenyl]sulfonyl}amino)-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

20

Step (A64a): Following a procedure analogous to step (A4a), the material from step (A50k) was coupled with [3-(2-chlorophenoxy)phenyl]phenylsulfonamide to give the title product. MS found (M+1)<sup>+</sup> 976.3.

25

**Example A65**

(3*S*,6*S*,9*S*,12*S*)-9-(cyclohexylmethyl)-12-(2,2-difluoroethyl)-3-isobutyl-6-[(1*R*)-1-methylpropyl]-1,4,7,10,13-pentaoxo-1-(2-pyrazinyl)-2,5,8,11-tetraazatetradecan-14-oic acid

30

Step (A65a): Following a procedure analogous to step (A4), the material from step (A50k) was treated with Dess-Martin reagent to obtain the title product. MS found (M+1)<sup>+</sup> 653.5.

35

**Example A66**

*N*-(4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-15-({[4'-methyl[1,1'-biphenyl]-3-yl]sulfonyl}amino)-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl)-2-pyrazinecarboxamide

40



5

Step (A66a): Following a procedure analogous to step (A4a), the material from step (A50k) was coupled with [(4'-methyl[1,1'-biphenyl]-3-yl)sulfonamide to give the title product. MS found (M+1)<sup>+</sup> 940.1.

10

#### Example A67

*N*-[15-({[3',5'-bis(trifluoromethyl)[1,1'-biphenyl]-3-yl]sulfonyl}amino)-4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-  
15 3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

Step (A67a): Following a procedure analogous to step (A4a), the material from step (A50k) was coupled with [3',5'-bis(trifluoromethyl)[1,1'-biphenyl]-3-yl]sulfonamide to  
20 give the title product. MS found (M+1)<sup>+</sup> 1061.8.

#### Example A68

*N*-[4-*sec*-butyl-15-[(5-[(4-cyanobenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl]amino]-7-(cyclohexylmethyl)-10-  
25 (2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

Step (A68a): Following a procedure analogous to step (A4a), the material from step (A50k) was coupled with {(4-cyanobenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonamide to  
30 give the title product. MS found (M+1)<sup>+</sup> 1001.9.

#### Example A69

*N*-[4-*sec*-butyl-15-[(5-[(2-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl]amino]-7-(cyclohexylmethyl)-10-  
35 (2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

Step (A69a): Following a procedure analogous to step (A4a),  
40 the material from step (A50k) was coupled with {5-[(2-

5 chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonamide to  
give the title product. MS found (M+1)<sup>+</sup> 1011.2.

**Example A70**

10 *N*-{4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-  
1-isobutyl-15-[(5-[(4-methoxybenzoyl)amino]-1,3,4-  
thiadiazol-2-yl)sulfonyl]amino]-2,5,8,11,12,15-hexaoxo-  
3,6,9,13-tetraazapentadec-1-yl}-2-pyrazinecarboxamide

15 Step (A70a): Following a procedure analogous to step (A4a),  
the material from step (A50k) was coupled with {5-[(4-  
methoxybenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonamide to  
give the title product. MS found (M+1)<sup>+</sup> 1006.8.

**Example A71**

20 *N*-{4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-  
1-isobutyl-15-[(5-[(3-methoxybenzoyl)amino]-1,3,4-  
thiadiazol-2-yl)sulfonyl]amino]-2,5,8,11,12,15-hexaoxo-  
3,6,9,13-tetraazapentadec-1-yl}-2-pyrazinecarboxamide

25 Step (A71a): Following a procedure analogous to step (A4a),  
the material from step (A50k) was coupled with {5-[(3-  
methoxybenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonamide to  
give the title product. MS found (M+1)<sup>+</sup> 1007.1.

**Example A72**

30 *N*-{4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-  
15-[(5-[(3,5-dimethylbenzoyl)amino]-1,3,4-thiadiazol-2-  
yl)sulfonyl]amino]-1-isobutyl-2,5,8,11,12,15-hexaoxo-  
3,6,9,13-tetraazapentadec-1-yl}-2-pyrazinecarboxamide

35 Step (A72a): Following a procedure analogous to step (A4a),  
the material from step (A50k) was coupled with {5-[(3,5-  
dimethylbenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonamide to  
give the title product. MS found (M+1)<sup>+</sup> 1007.1.

5 **Example A73**

*N*-(4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-  
1-isobutyl-2,5,8,11,12,15-hexaoxo-15-[(3-  
phenoxyphenyl)sulfonyl]amino)-3,6,9,13-tetraazapentadec-1-  
yl)-2-pyrazinecarboxamide

10

Step (A73a): Following a procedure analogous to step (A4a),  
the material from step (A50k) was coupled with (3-  
phenoxyphenyl)sulfonamide to give the title product. MS  
found (M+1)<sup>+</sup> 941.8.

15

**Example A74**

6-*sec*-butyl-9-(cyclohexylmethyl)-12-ethyl-3-isobutyl-  
1,4,7,10,13-pentaoxo-1-(2-pyrazinyl)-2,5,8,11-  
tetraazatetradecan-14-oic acid

20

Step (A74a): Following a procedure analogous to step  
(A65a), the material from step (A50k) was treated with  
Dess-Martin reagent to give the title product. MS found  
(M+1)<sup>+</sup> 617.4.

25

**Example A75**

*N*-{4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-  
1-isobutyl-15-[(5-[(3-methylbutanoyl)amino]-1,3,4-  
thiadiazol-2-yl)sulfonyl]amino)-2,5,8,11,12,15-hexaoxo-  
3,6,9,13-tetraazapentadec-1-yl}-2-pyrazinecarboxamide

30

Step (A75a): Following a procedure analogous to step (A4a),  
the title compound was obtained. MS found (M+1)<sup>+</sup> 957.0.

35

**Example A76**

*N*-[4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-  
15-([5-(hexanoylamino)-1,3,4-thiadiazol-2-  
yl)sulfonyl]amino)-1-isobutyl-2,5,8,11,12,15-hexaoxo-  
3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

5 Step (A76a): Following a procedure analogous to step (A4a),  
the title compound was obtained. MS found (M+1)<sup>+</sup> 971.0.

**Example A77**

10 Methyl (3*S*,6*S*,9*S*,12*S*)-9-(cyclohexylmethyl)-12-(2,2-  
difluoroethyl)-3-isobutyl-6-[(1*R*)-1-methylpropyl]-  
1,4,7,10,13,14-hexaoxo-1-(2-pyrazinyl)-2,5,8,11,15-  
pentaazaheptadecan-17-oate

15 Step (A77a): Following a procedure analogous to step (A4a),  
the title compound was obtained. MS found (M+1)<sup>+</sup> 724.4.

**Example A78**

20 *N*-[4-*sec*-butyl-15-{[(3-chloro-5-{[(3-  
chlorobenzoyl)amino]sulfonyl}phenyl)sulfonyl]amino}-7-  
(cyclohexylmethyl)-10-ethyl-1-isobutyl-2,5,8,11,12,15-  
hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-  
pyrazinecarboxamide

25 Step (A78a): Following a procedure analogous to step (A4a),  
the title compound was obtained. MS found (M+1)<sup>+</sup> 1066.1.

**Example A79**

30 *N*-[4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-  
1-isobutyl-2,5,8,11,12,15-hexaoxo-15-({[4'-  
(trifluoromethyl)[1,1'-biphenyl]-3-yl]sulfonyl}amino)-  
3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

35 Step (A79a): Following a procedure analogous to step (A4a),  
the title compound was obtained. MS found (M+1)<sup>+</sup> 993.9.

**Example A80**

40 *N*-[15-([1,1'-biphenyl]-3-ylsulfonyl)amino]-4-*sec*-butyl-7-  
(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-  
2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-  
pyrazinecarboxamide

5

Step (A80a): Following a procedure analogous to step (A4a), the title compound was obtained. MS found (M+1)<sup>+</sup> 926.1.

**Example A81**

10 *N*-[4-*sec*-butyl-15-[(5-[(4-*tert*-butylbenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl]amino]-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

15 Step (A81a): Following a procedure analogous to step (A4a), the title compound was obtained. MS found (M+1)<sup>+</sup> 1033.1.

**Example A82**

20 *N*-[4-*sec*-butyl-15-[(3-chloro-5-[(3-methylbutanoyl)amino]sulfonyl)phenyl)sulfonyl]amino]-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

25 Step (A82a): Following a procedure analogous to step (A4a), the title compound was obtained. MS found (M+1)<sup>+</sup> 1047.7.

**Example A83**

30 *N*-{(1*S*,4*S*,7*S*,10*S*)-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-14-[4-(4-methoxyphenyl)-5-(trifluoromethyl)-4*H*-1,2,4-triazol-3-yl]-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-tetraazatetradec-1-yl}-2-pyrazinecarboxamide

35 Step (A83a): Following a procedure analogous to step (A4a), the title compound was obtained. MS found (M+1)<sup>+</sup> 907.8.

**Example A84**

40 *N*-{4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-15-[(5-[(4-ethylbenzoyl)amino]-1,3,4-thiadiazol-2-

5 yl)sulfonyl)amino]-1-isobutyl-2,5,8,11,12,15-hexaoxo-  
3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

Step (A84a): Following a procedure analogous to step (A4a),  
the title compound was obtained. MS found (M+1)<sup>+</sup> 1005.2.

10

**Example A85**

*N*-[4-*sec*-butyl-15-[(5-[(4-chlorobenzoyl)amino]-1,3,4-  
thiadiazol-2-yl)sulfonyl)amino]-7-(cyclohexylmethyl)-10-  
(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-  
15 3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

Step (A85a): Following a procedure analogous to step (A4a),  
the title compound was obtained. MS found (M+1)<sup>+</sup> 1011.5.

20

**Example A86**

*N*-[4-*sec*-butyl-7-(cyclohexylmethyl)-15-[(5-[(3,5-  
difluorobenzoyl)amino]-1,3,4-thiadiazol-2-  
yl)sulfonyl)amino]-10-(2,2-difluoroethyl)-1-isobutyl-  
2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-  
25 pyrazinecarboxamide

Step (A86a): Following a procedure analogous to step (A4a),  
the title compound was obtained. MS found (M+1)<sup>+</sup> 1013.1.

30

**Example A87**

*N*-[4-*sec*-butyl-15-[(5-[(3-chlorobenzoyl)amino]-1,3,4-  
thiadiazol-2-yl)sulfonyl)amino]-7-(cyclohexylmethyl)-10-  
(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-  
3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide  
35

Step (A87a): Following a procedure analogous to step (A4a),  
the title compound was obtained. MS found (M+1)<sup>+</sup> 1011.3.

5

**Example A88**

*N*-{(1*S*,4*S*,7*S*,10*S*)-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-tetraazahexadec-15-en-1-yl}-2-pyrazinecarboxamide

10 Step (A88a): Following a procedure analogous to steps (A1) and (A4a). The detailed procedure can be found in Han, W. et.; *Bioorg. Med. Chem. Lett.* 10, 711-713, 2000 and is hereby incorporated by reference in its entirety. The title compound was obtained. MS found (M+1)<sup>+</sup> 656.4.

15

**Example A89**

*N*-{(1*S*,4*S*,7*S*,10*S*)-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-tetraazahexadec-15-yn-1-yl}-2-pyrazinecarboxamide

20

Step (A89a): Following a procedure analogous to step (A88a), the title compound was obtained. MS found (M+1)<sup>+</sup> 654.5.

25

**Example A90**

*tert*-butyl (3*S*,6*S*,9*S*,12*S*)-9-(cyclohexylmethyl)-12-ethyl-3-isobutyl-6-[(1*R*)-1-methylpropyl]-1,4,7,10,13,14-hexaoxo-1-(2-pyrazinyl)-2,5,8,11,15-pentaazaheptadecan-17-oate

30

Step (A90a): Following a procedure analogous to step (A88a), the title compound was obtained. MS found (M+1)<sup>+</sup> 730.5.

35

**Example A91**

*N*-{(1*S*,4*S*,7*S*,10*S*)-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-14-phenyl-3,6,9,13-tetraazatetradec-1-yl}-2-pyrazinecarboxamide

5 Step (A91a): Following a procedure analogous to step  
(A88a), the title compound was obtained. MS found (M+1)<sup>+</sup>  
706.4.

**Example A92**

10 *N*-((1*S*)-1-[[[(1*S*,2*R*)-1-[[[(1*S*)-1-(cyclohexylmethyl)-2-  
{[(1*S*)-1-ethyl-2,3-dioxo-3-(1-pyrrolidinyl)propyl]amino}-2-  
oxoethyl)amino]carbonyl}-2-methylbutyl)amino]carbonyl}-3-  
methylbutyl)-2-pyrazinecarboxamide

15 Step (A92a): Following a procedure analogous to step  
(A88a), the title compound was obtained. MS found (M+1)<sup>+</sup>  
670.3

**Example A93**

20 *N*-{(1*S*,4*S*,7*S*,10*S*)-7-(cyclohexylmethyl)-10-ethyl-15,15,15-  
trifluoro-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-  
penta-3,6,9,13-tetraazapentadec-1-yl}-2-  
pyrazinecarboxamide

25 Step (A93a): Following a procedure analogous to step  
(A88a), the title compound was obtained. MS found (M+1)<sup>+</sup>  
698.2.

**Example A94**

30 *N*-{(1*S*,4*S*,7*S*,10*S*)-15-amino-7-(cyclohexylmethyl)-10-ethyl-1-  
isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12,15-hexa-3,6,9,13-  
tetraazapentadec-1-yl}-2-pyrazinecarboxamide

Step (A94a): Following a procedure analogous to step  
35 (A88a), the title compound was obtained. MS found (M+1)<sup>+</sup>  
673.4.

**Example A95**

40 (3*S*,6*S*,9*S*,12*S*,16*S*)-9-(cyclohexylmethyl)-12-ethyl-3-  
isobutyl-16-methyl-6-[(1*R*)-1-methylpropyl]-1,4,7,10,13,14-



5 hexa-1-(2-pyrazinyl)-2,5,8,11,15-pentaazaheptadecan-17-  
oic acid

Step (A95a): Following a procedure analogous to step  
(A88a), the title compound was obtained. MS found (M+1)<sup>+</sup>  
10 688.5.

**Example A96**

*N*-[9-*sec*-butyl-6-(cyclohexylmethyl)-3-ethyl-12-isobutyl-  
2,5,8,11,14-pentaoxo-14-(2-pyrazinyl)-4,7,10,13-  
15 tetraazatetradec-1-anoyl]aspartic acid

Step (A96a): Following a procedure analogous to step  
(A88a), the title compound was obtained. MS found (M+1)<sup>+</sup>  
732.4.  
20

**Example A97**

(3*S*,6*S*,9*S*,12*S*)-9-(cyclohexylmethyl)-12-ethyl-3-isobutyl-6-  
[(1*R*)-1-methylpropyl]-1,4,7,10,13,14-hexa-1-(2-  
pyrazinyl)-2,5,8,11,15-pentaazaoctadecan-18-oic acid  
25

Step (A97a): Following a procedure analogous to step  
(A88a), the title compound was obtained. MS found (M+1)<sup>+</sup>  
688.5.

30 **Example B1**

1,1-dimethylethyl *N*-(2-pyrazinylcarbonyl)-*L*-leucyl-*L*-  
isoleucyl-(4*R*)-4-(phenylmethoxy)-*L*-prolyl-5,5-difluoro-2-  
oxo-(3*S*)-3-aminopentanoylglycine

35 Step (B1a): Following a procedure analogous to step (A1)  
and (A50), the compound **32a** {Pz(CO)-Lue-Ile-Hyp(OBn)-  
NHCH(CH<sub>2</sub>CHF<sub>2</sub>)CH(OH)CO<sub>2</sub>Me} was obtained as crystalline  
solid. MS found (M+1)<sup>+</sup> 719.1.

40 Step (B1b): Following a procedure analogous to step (A2e),  
the product from step (B1a) was treated with LiOH to

5 provide the corresponding  $\alpha$ -hydroxyacid as crystalline solid. MS found (M+1)<sup>+</sup> 715.1; (M-1)<sup>-</sup> 713.

Step (B1c): Following a procedure analogous to step (A1j) and step (A1k), the above material was coupled with Gly-  
10 OtBu followed by oxidation to provide the title product (Scheme 5, **33**) as crystalline solid. MS found (M+1)<sup>+</sup> 816.4.

#### Example B2

15 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-di fluoro-2-oxo-(3S)-3-aminopentanoylglycine

Step (B2a): Following a procedure analogous to Step (A1l),  
20 the material from Step (B1c) was treated with TFA to afford title product (Scheme 5, **34**) as a white solid. MS found (M+1)<sup>+</sup> 760.3.

#### Example B3

25 (4R)-1-[N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl]-N-[(1S)-1-(2,2-difluoroethyl)-2,3-dioxo-3-[(2H)-tetrazol-5-yl methyl)amino]propyl]-4-(phenylmethoxy)-L-prolinamide

Step (B3a): Following a procedure analogous to Steps (A2f-  
30 g), the material from Step (B1b) was coupled with aminotetrazole followed by oxidation to give the title product as a white solid. MS found (M+1)<sup>+</sup> 784.4.

#### Example B4

35 (4R)-N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-N-[(1S)-1-(2,2-difluoroethyl)-3-methoxy-2,3-dioxopropyl]-4-(phenylmethoxy)-L-prolinamide

Step (B4a): Following a procedure analogous to step (A2g),  
40 the material from (B1a) was oxidized to the desired product. MS found (M+1)<sup>+</sup> 717.3.

5

**Example B5**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[(3-chlorophenyl)sulfonyl]glycinamide

10

Step (B5a): Following a procedure analogous to Step (A4a), the material from Step (B2a) was coupled with 3-chlorophenylsulfonamide to afford the title product as a white solid. MS found (M+1)<sup>+</sup> 933.3.

15

**Example B6**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[(5-carboxy-2-chlorophenyl)sulfonyl]glycinamide

20

Step (B6a): Following a procedure analogous to step (4a), the material from step (B2a) was coupled with 5-carboxy-2-chlorophenylsulfonamide to afford title product as white solid. MS found (M+1)<sup>+</sup> 978.2

25

**Example B7**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[(5-acetylamino)1,3,4-thiadiazol-2-yl)sulfonyl]glycinamide

30

Step (B7a): Following a procedure analogous to step (4a), the material from step (B2a) was coupled with N-[(5-acetylamino)1,3,4-thiadiazol-2-yl)sulfonamide to afford title product as white solid. MS found (M+1+H<sub>2</sub>O)<sup>+</sup> 982.5.

35

**Example B8**

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[3,5-dichlorophenyl)sulfonyl]glycinamide

40

5

Step (B8a): Following a procedure analogous to step (4a), the material from step (B2a) was coupled with (3,5-dichlorophenyl) sulfonamide to afford title product as white solid. MS found (M+1)<sup>+</sup> 967.6.

10

#### Example B9

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl N-(4-methyl-3-nitrophenyl)sulfonyl]-glycinamide

15

Step (B9a): Following a procedure analogous to step (4a), the material from step (B2a) was coupled with (4-methyl-3-nitrophenyl) sulfonamide to afford title product as white solid. MS found (M+1)<sup>+</sup> 958.4.

20

#### Example B10

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl N-(3-carboxyl-4-chloro-2-fluorophenyl)sulfonyl]-glycinamide

25

Step (B10a): Following a procedure analogous to step (4a), the material from step (B2a) was coupled with (3-carboxyl-4-chloro-2-fluorophenyl)sulfonamide to afford title product as white solid. MS found (M+1)<sup>+</sup> 995.4.

30

#### Example B11

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl N-[(3-chloro-4-acetylamino)phenyl]sulfonyl]-glycinamide

35

Step (B11a): Following a procedure analogous to step (4a), the material from step (B2a) was coupled with (3-chloro-4-

40

5 acetylamino)phenyl sulfonamide to afford title product as  
white solid. MS found (M+1)<sup>+</sup> 1116.5.

**Example B12**

10 *N*-((1*S*)-1-[[[(1*S*,2*R*)-1-[[ (2*S*,4*R*)-2-({[(1*S*)-3-({2-[(3-  
[(benzoylamino)sulfonyl]-5-chlorophenyl)sulfonyl)amino]-2-  
oxoethyl)amino)-1-(2,2-difluoroethyl)-2,3-  
dioxopropyl]amino}carbonyl)-4-  
(benzyloxy)pyrrolidinyl]carbonyl]-2-  
methylbutyl)amino]carbonyl]-3-methylbutyl)-2-  
15 pyrazinecarboxamide

Step (B12a): Following a procedure analogous to step (B7a),  
the title compound was obtained. MS found (M+1)<sup>+</sup> 1117.4.

**Example B13**

20 *tert*-butyl ({(3*S*)-3-[( (2*S*,4*R*)-4-(benzyloxy)-1-[(2*S*)-3-  
methyl-2-({(2*S*)-3-methyl-2-[(2-  
pyrazinylcarbonyl)amino]butanoyl)amino)butanoyl]pyrrolidiny  
l}carbonyl)amino]-5,5-difluoro-2-oxopentanoyl)amino)acetate

25 Step (B13a): Following a procedure analogous to step (B7a),  
the title compound was obtained. MS found (M+1)<sup>+</sup> 788.9.

**Example B14**

30 *N*-((1*S*)-1-[[[(1*S*,2*R*)-1-[[ (2*S*,4*R*)-4-(benzyloxy)-2-({[(1*S*)-3-  
[(2-[(3-chloro-4-methylphenyl)sulfonyl]amino]-2-  
oxoethyl)amino]-1-(2,2-difluoroethyl)-2,3-  
dioxopropyl]amino}carbonyl)pyrrolidinyl]carbonyl]-2-  
methylbutyl)amino]carbonyl]-3-methylbutyl)-2-  
35 pyrazinecarboxamide

Step (B14a): Following a procedure analogous to step (B7a),  
the title compound was obtained. MS found (M+1)<sup>+</sup> 948.3.

5 **Example B15**

*N*-((1*S*)-1-[[[(1*S*,2*R*)-1-[(2*S*,4*R*)-4-(benzyloxy)-2-([(1*S*)-3-  
 ({2-[(5-[(3-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-  
 yl)sulfonyl)amino]-2-oxoethyl)amino)-1-(2,2-difluoroethyl)-  
 2,3-dioxopropyl]amino)carbonyl]pyrrolidinyl]carbonyl}-2-  
 10 methylbutyl)amino]carbonyl}-3-methylbutyl)-2-  
 pyrazinecarboxamide

Step (B15a): Following a procedure analogous to step (B7a),  
 the title compound was obtained. MS found (M+1)<sup>+</sup> 1061.3.

15

**Example B16**

Methyl ((3*S*)-3-[[[(2*S*,4*R*)-4-(benzyloxy)-1-[(2*S*,3*R*)-3-  
 methyl-2-[(2*S*)-4-methyl-2-[(2-  
 20 pyrazinylcarbonyl)amino]pentanoyl)amino)pentanoyl]pyrrolidi  
 nyl]carbonyl)amino]-5,5-difluoro-2-  
 oxopentanoyl]amino)acetate

Step (B16a): Following a procedure analogous to step (B7a),  
 the title compound was obtained. MS found (M+1)<sup>+</sup> 774.6.

25

**Example B17**

*N*-((1*S*)-1-[[[(1*S*,2*R*)-1-[(2*S*,4*R*)-4-(benzyloxy)-2-([(1*S*)-3-  
 [(2-[(2,4-dichloro-5-methylphenyl)sulfonyl]amino]-2-  
 30 oxoethyl)amino]-1-(2,2-difluoroethyl)-2,3-  
 dioxopropyl]amino)carbonyl]pyrrolidinyl]carbonyl}-2-  
 methylbutyl)amino]carbonyl}-3-methylbutyl)-2-  
 pyrazinecarboxamide

Step (B17a): Following a procedure analogous to step (B7a),  
 35 the title compound was obtained. MS found (M+1)<sup>+</sup> 982.6.

**Example B18**

*N*-[(1*S*)-1-([(1*S*,2*R*)-1-[(2*S*,4*R*)-4-(benzyloxy)-2-([(1*S*)-1-  
 (2,2-difluoroethyl)-3-[(2-[(3,4-  
 40 difluorophenyl)sulfonyl]amino]-2-oxoethyl)amino]-2,3-  
 dioxopropyl]amino)carbonyl]pyrrolidinyl]carbonyl)-2-

5 methylbutyl]amino}carbonyl)-3-methylbutyl]-2-  
pyrazinecarboxamide

Step (B18a): Following a procedure analogous to step (B7a),  
the title compound was obtained. MS found (M+1)<sup>+</sup> 935.7.

10

**Example B19**

Methyl 5-({[({(3*S*)-3-[({(2*S*,4*R*)-4-(benzyloxy)-1-[(2*S*,3*R*)-3-  
methyl-2-({(2*S*)-4-methyl-2-[(2-  
pyrazinylcarbonyl)amino]pentanoyl)amino)pentanoyl]pyrrolidi  
15 nyl}carbonyl)amino]-5,5-difluoro-2-  
oxopentanoyl)amino)acetyl]amino)sulfonyl)-2,4-  
dichlorobenzoate

Step (B19a): Following a procedure analogous to step (B7a),  
20 the title compound was obtained. MS found (M+1)<sup>+</sup> 1026.7.

**Example B20**

*N*-{(1*S*)-1-[({(1*S*,2*R*)-1-[({(2*S*,4*R*)-4-(benzyloxy)-2-[({(1*S*)-1-  
(2,2-difluoroethyl)-3-[2-({[4-(3,5-dimethyl-1-  
25 piperidinyl)-3-nitrophenyl]sulfonyl)amino)-2-  
oxoethyl]amino)-2,3-  
dioxopropyl)amino]carbonyl]pyrrolidinyl)carbonyl]-2-  
methylbutyl]amino)carbonyl]-3-methylbutyl]-2-  
pyrazinecarboxamide

30

Step (B20a): Following a procedure analogous to step (B7a),  
the title compound was obtained. MS found (M+1)<sup>+</sup> 1056.0.

**Example B21**

35 *N*-[(1*S*)-1-({[(1*S*,2*R*)-1-[({(2*S*,4*R*)-4-(benzyloxy)-2-[({(1*S*)-1-  
(2,2-difluoroethyl)-3-[2-({[3-nitrophenyl]sulfonyl]amino)-  
2-oxoethyl)amino]-2,3-  
dioxopropyl)amino)carbonyl]pyrrolidinyl)carbonyl]-2-  
methylbutyl]amino)carbonyl)-3-methylbutyl]-2-  
40 pyrazinecarboxamide

5 Step (B21a): Following a procedure analogous to step (B7a),  
the title compound was obtained. MS found (M+1)<sup>+</sup> 944.8.

**Example B22**

10 N-{(1*S*)-1-[({(1*S*,2*R*)-1-[(2*S*,4*R*)-4-(benzyloxy)-2-[(1*S*)-1-(  
(2,2-difluoroethyl)-3-{[2-({[5-(hexanoylamino)-1,3,4-  
thiadiazol-2-yl]sulfonyl}amino)-2-oxoethyl]amino}-2,3-  
dioxopropyl)amino]carbonyl]pyrrolidinyl)carbonyl]-2-  
methylbutyl}amino)carbonyl]-3-methylbutyl}-2-  
pyrazinecarboxamide

15

Step (B22a): Following a procedure analogous to step (B7a),  
the title compound was obtained. MS found (M+1)<sup>+</sup> 1021.1.

**Example B23**

20 5-({[({(3*S*)-3-[({(2*S*,4*R*)-4-(benzyloxy)-1-[(2*S*,3*R*)-3-methyl-  
2-({(2*S*)-4-methyl-2-[(2-  
pyrazinylcarbonyl)amino]pentanoyl}amino)pentanoyl]pyrrolidi  
nyl}carbonyl)amino]-5,5-difluoro-2-  
oxopentanoyl}amino)acetyl]amino)sulfonyl)-2,4-  
25 dichlorobenzoic acid

Step (B23a): Following a procedure analogous to step (B7a),  
the title compound was obtained. MS found (M+1)<sup>+</sup> 1012.6.

30

**Example C1**

N-[[5-(4-chlorophenyl)-2-furanyl]carbonyl]-L-isoleucyl-3-  
cyclohexylalanyl-2-oxo-3-aminopentanoylglycine

35 Step (C1a): Following the procedures analogous to step (A1)  
and step (A2), the title product was obtained as  
crystalline solid. MS found (M+1)<sup>+</sup> 659.4.

**Example C2**

40 N-[[5-(4-chlorophenyl)-2-furanyl]carbonyl]-L-isoleucyl-3-  
cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-  
[(trifluoromethyl)sulfonyl]glycinamide



5

Step (C2a): Following a procedure analogous to step (A4a), the material from step (C1a) was coupled with trifluoromethylsulfonamide to afford the title product as crystalline solid. MS found (M+1)<sup>+</sup> 790.3.

10

**Example C3**

N-[[5-(4-chlorophenyl)-2-furanyl]carbonyl]-Lisoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(3,5-dichlorophenyl)sulfonyl]glycinamide

15

Step (C3a): Following the procedures analogous to step (A4a), the material from step (C1a) was coupled with 3,5-dichlorophenyl)sulfonamide to afford the title product as crystalline solid. MS found (M+1)<sup>+</sup> 866.6.

20

**Example C4**

N-[[5-(4-chlorophenyl)-2-furanyl]carbonyl]-Lisoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(3-nitrophenyl)sulfonyl]glycinamide

25

Step (C4a): Following the procedures analogous to step (A4a), the material from step (C1a) was coupled with -(3-nitrophenyl)sulfonamide to afford the title product as crystalline solid. MS found (M+1)<sup>+</sup> 841.3.

30

**Example C5**

(4R)-1-[[5-(4-chlorophenyl)-2-furanyl]carbonyl]-L-isoleucyl-N-[(1S)-1-(2,2-difluoroethyl)-2,3-dioxo-3-[(2H-tetrazol-5-ylmethyl)amino]propyl]-4-(phenylmethoxy)-L-prolinamide

35

Step (C5a): Following the procedures analogous to steps (A50) and (B1), the title compound was obtained as crystalline solid. MS found (M+1)<sup>+</sup> 769.3.

5 **Example C6**

(2*S*,4*R*)-4-(benzyloxy)-*N*-{ (1*S*)-1-(2,2-difluoroethyl)-2,3-dioxo-3-[(2*H*-tetraazol-5-ylmethyl)amino]propyl}-1-((2*S*,3*R*)-3-methyl-2-{[(9-oxo-9*H*-fluoren-1-yl)carbonyl]amino}pentanoyl)-2-pyrrolidinecarboxamide

10

Step (C6a): Following the procedures analogous to steps (A50) and (B1), the title compound was obtained as crystalline solid. MS found (M+1)<sup>+</sup> 771.5.

15 **Example C7**

*tert*-butyl {[ (3*S*)-3-({[(2*S*,4*R*)-4-(benzyloxy)-1-((2*S*,3*R*)-3-methyl-2-{[(9-oxo-9*H*-fluoren-1-yl)carbonyl]amino}pentanoyl)pyrrolidinyl]carbonyl}amino)-5,5-difluoro-2-oxopentanoyl]amino}acetate

20

Step (C7a): Following the procedures analogous to steps (A50) and (B1), the title compound was obtained as crystalline solid. MS found (M+1)<sup>+</sup> 803.4.

25 **Example C8**

{[(3*S*)-3-({[(2*S*,4*R*)-4-(benzyloxy)-1-((2*S*,3*R*)-3-methyl-2-{[(9-oxo-9*H*-fluoren-1-yl)carbonyl]amino}pentanoyl)pyrrolidinyl]carbonyl}amino)-5,5-difluoro-2-oxopentanoyl]amino}acetic acid

30

Step (C8a): Following the procedures analogous to steps (A50) and (B1), the title compound was obtained as crystalline solid. MS found (M+1)<sup>+</sup> 747.3.

35 **Example C9**

(2*S*,4*R*)-*N*-[(1*S*)-3-{[2-({[5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl}amino)-2-oxoethyl]amino}-1-(2,2-difluoroethyl)-2,3-dioxopropyl]-4-(benzyloxy)-1-((2*S*,3*R*)-3-methyl-2-{[(9-oxo-9*H*-fluoren-1-yl)carbonyl]amino}pentanoyl)-2-pyrrolidinecarboxamide

40

5 Step (C9a): Following the procedures analogous to steps  
(A50) and (B1), the title compound was obtained as  
crystalline solid. MS found (M+1)<sup>+</sup> 951.2.

**Example C10**

10 (2*S*,4*R*)-4-(benzyloxy)-*N*-((1*S*)-1-(2,2-difluoroethyl)-3-{{2-  
({[5-(hexanoylamino)-1,3,4-thiadiazol-2-yl]sulfonyl}amino)-  
2-oxoethyl}amino)-2,3-dioxopropyl)-1-((2*S*,3*R*)-3-methyl-2-  
{{[(9-oxo-9*H*-fluoren-1-yl)carbonyl]amino}pentanoyl)-2-  
pyrrolidinecarboxamide

15

Step (C10a): Following the procedures analogous to steps  
(A50) and (B1), the title compound was obtained as  
crystalline solid. MS found (M+1)<sup>+</sup> 1007.9.

20

**Example C11**

((2*S*,4*R*)-4-(benzyloxy)-*N*-[(1*S*)-3-({2-[(5-[(4-  
chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl]sulfonyl)amino]-  
2-oxoethyl}amino)-1-(2,2-difluoroethyl)-2,3-dioxopropyl]-1-  
((2*S*,3*R*)-3-methyl-2-{{[(9-oxo-9*H*-fluoren-1-  
25 yl)carbonyl]amino}pentanoyl)-2-pyrrolidinecarboxamide

Step (C11a): Following the procedures analogous to steps  
(A50) and (B1), the title compound was obtained as  
30 crystalline solid. MS found (M+1)<sup>+</sup> 1048.3.

**Example C12**

(2*S*,4*R*)-4-(benzyloxy)-*N*-[(1*S*)-1-(2,2-difluoroethyl)-3-({2-  
[({5-[(4-ethylbenzoyl)amino]-1,3,4-thiadiazol-2-  
35 yl]sulfonyl)amino]-2-oxoethyl}amino)-2,3-dioxopropyl]-1-  
((2*S*,3*R*)-3-methyl-2-{{[(9-oxo-9*H*-fluoren-1-  
yl)carbonyl]amino}pentanoyl)-2-pyrrolidinecarboxamide

Step (C12a): Following the procedures analogous to steps  
40 (A50) and (B1), the title compound was obtained as  
crystalline solid. MS found (M+1)<sup>+</sup> 1041.8.

5

**Example C13**

*tert*-butyl {[ (3*S*)-3-({ [(2*S*,4*R*)-4-(benzyloxy)-1-((2*S*,3*R*)-2-  
 {[5-(4-chlorophenyl)-2-furoyl]amino}-3-  
 methylpentanoyl)pyrrolidinyl]carbonyl}amino)-5,5-difluoro-  
 2-oxopentanoyl]amino}acetate

Step (C13a): Following the procedures analogous to steps  
 (A50) and (B1), the title compound was obtained. MS found  
 (M+1)<sup>+</sup> 801.9.

15

**Example C14**

{ [(3*S*)-3-({ [(2*S*,4*R*)-4-(benzyloxy)-1-((2*S*,3*R*)-2-  
 {[5-(4-  
 chlorophenyl)-2-furoyl]amino}-3-  
 methylpentanoyl)pyrrolidinyl]carbonyl}amino)-5,5-difluoro-  
 2-oxopentanoyl]amino}acetic acid

Step (C14a): Following the procedures analogous to steps  
 (A50) and (B1), the title compound was obtained. MS found  
 (M+1)<sup>+</sup> 746.0.

**Example C15**

(2*S*,4*R*)-*N*-[(1*S*)-3-{[2-({[5-(acetylamino)-1,3,4-thiadiazol-  
 2-yl]sulfonyl}amino)-2-oxoethyl]amino}-1-(2,2-  
 difluoroethyl)-2,3-dioxopropyl]-4-(benzyloxy)-1-((2*S*,3*R*)-2-  
 {[5-(4-chlorophenyl)-2-furoyl]amino}-3-methylpentanoyl)-2-  
 pyrrolidinecarboxamide

Step (C15a): Following the procedures analogous to steps  
 (A50) and (B1), the title compound was obtained. MS found  
 (M+1)<sup>+</sup> 950.1.

**Example C16**

(2*S*,4*R*)-4-(benzyloxy)-*N*-[(1*S*)-3-({2-[(5-[(3-  
 chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl]sulfonyl)amino]-  
 2-oxoethyl}amino)-1-(2,2-difluoroethyl)-2,3-dioxopropyl]-1-

5 ((2*S*,3*R*)-2-{[5-(4-chlorophenyl)-2-furoyl]amino}-3-methylpentanoyl)-2-pyrrolidinecarboxamide

Step (C16a): Following the procedures analogous to steps (A50) and (B1), the title compound was obtained. MS found  
10 (M+1)<sup>+</sup> 1046.7.

**Example C17**

(2*S*,4*R*)-4-(benzyloxy)-*N*-[(1*S*)-3-({2-([1,1'-biphenyl]-3-ylsulfonyl)amino}-2-oxoethyl)amino]-1-(2,2-difluoroethyl)-  
2,3-dioxopropyl]-1-((2*S*,3*R*)-2-{[5-(4-chlorophenyl)-2-furoyl]amino}-3-methylpentanoyl)-2-pyrrolidinecarboxamide  
15

Step (C17a): Following the procedures analogous to steps (A50) and (B1), the title compound was obtained. MS found  
(M+1)<sup>+</sup> 961.2.

20

**Example D1**

*N*-{(1*S*,4*S*,7*S*)-10-allyl-7-(cyclohexylmethyl)-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-tetraaza-hexadec-15-en-1-yl}-2-pyrazinecarboxamide  
25

Step (D1a): The  $\alpha$ -hydroxyl  $\beta$ -allyl homoallylglycinamide was prepared according to the following reference disclosed in Han, W. et. al, *Bioorg. & Med. Chem Lett.*, 10, 711-713, **2000**, which is hereby incorporated by reference.

30 (D1b): Tripeptide R-Leu-Ile-Cha-OH was prepared following a procedure analogous to Steps (A2a-h).

(D1c): Following a procedure analogous to Step (A1j), the product from (D1a) and (D1b) was coupled to give the desired  $\alpha$ -hydroxyamide.

35 (D1d): Following a procedure analogous to Step (A2g), the above  $\alpha$ -hydroxyamide was converted to the desired product. MS found (M+1)<sup>+</sup> 668.3.

5

**Example D2**

(6*S*,9*S*,12*S*)-*N*,3-diallyl-6-(cyclohexylmethyl)-12-isobutyl-9-  
[(1*R*)-1-methylpropyl]-2,5,8,11,14-pentaoxo-16,16-diphenyl-  
4,7,10,13-tetraazahexadecan-1-amide

10 Step (D2a): Following a procedure analogous to Steps (D1a-  
d), the title compound was obtained. MS found (M+1)<sup>+</sup> 770.9.

**Example D3**

15 (4*S*,7*S*,10*S*)-*N*,13-diallyl-10-(cyclohexylmethyl)-4-isobutyl-  
7-[(1*R*)-1-methylpropyl]-2,5,8,11,14-pentaoxo-3,6,9,12-  
tetraazapentadecan-15-amide

20 Step (D3a): Following a procedure analogous to Steps (D1a-  
d), the title compound was obtained. MS found (M+1)<sup>+</sup> 604.1.

**Example D4**

25 *N*-{(1*S*,4*S*,7*S*)-10-allyl-7-(cyclohexylmethyl)-1-isobutyl-4-  
[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-  
tetraazahexadec-15-en-1-yl}-2-pyridinecarboxamide

Step (D4a): Following a procedure analogous to to Steps  
(D1a-d), the title compound was obtained. MS found (M+1)<sup>+</sup>  
667.4.

30

**Example D5**

*N*-{(1*S*,4*S*,7*S*)-10-allyl-7-(cyclohexylmethyl)-1-isobutyl-4-  
[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-  
tetraazahexadec-15-en-1-yl}nicotinamide

35 Step (D5a): Following a procedure analogous to to Steps  
(D1a-d), the title compound was obtained. MS found (M+1)<sup>+</sup>  
667.4.

**Example D6**

40 *N*-{(1*S*,4*S*,7*S*)-10-allyl-7-(cyclohexylmethyl)-1-isobutyl-4-  
[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-



5

**Example D10**

{3-[(1-[3-methyl-2-[(4-methyl-2-[(2-pyrazinylcarbonyl)amino]pentanoyl}amino)pentanoyl]-octahydro-1*H*-indol-2-yl}carbonyl)amino]-2-oxopentanoyl}amino)acetic acid

10

(D10a): The peptide pyrazinecarbonyl-Leu-Ile-octahydroindazole carboxylic acid was prepared following a procedure analogous to Steps (A2a-h).

(D10b): Following a procedure analogous to Steps (A1j-l), the above peptide was coupled with the product from (A1d) and converted to the desired product. MS found (M+1)+ 672.4.

**Example D11**

tert-butyl {3-[(1-[3-methyl-2-[(4-methyl-2-[(2-pyrazinylcarbonyl)amino]pentanoyl}amino)-pentanoyl]octahydro-1*H*-indol-2-yl}carbonyl)amino]-2-oxopentanoyl}amino)acetate

Step (D11a): Following a procedure analogous to Steps (D10a-b), the title compound was obtained. MS found (M+1)+ 728.5.

**Example D12**

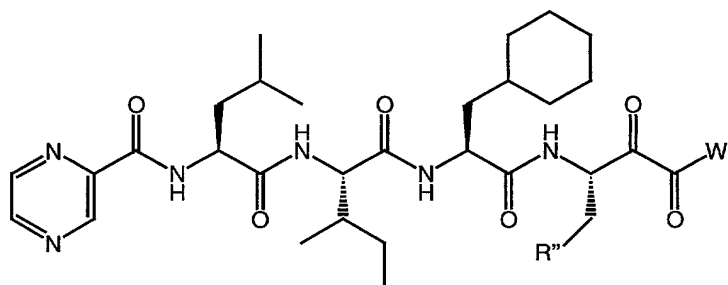
(3*S*,6*S*,9*S*,12*S*)-6-(cyclohexylmethyl)-3-ethyl-12-isobutyl-9-[(1*R*)-1-methylpropyl]-2,5,8,11,14-pentaoxo-16,16-diphenyl-4,7,10,13-tetraazahexadecan-1-oic acid

(D12a): Tripeptide R-Leu-Ile-Cha-OH was prepared following a procedure analogous to Steps (A2a-h).

(D12b): Following a procedure analogous to Step (A1j), the above tripeptide was coupled to the product from (A1d) to give the desired  $\alpha$ -hydroxyester.

((D12c): Following a procedure analogous to Steps (A2e) and (A2g), the above material was converted to the desired product. MS found (M+1)+ 719.6.



**Table 1**

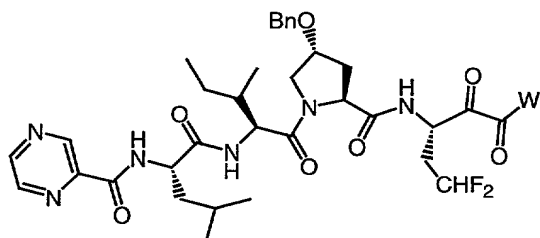
Ex #	R''	W''	(M+1) +
A1	Me	Glycine	674.4
A2	Me	2H-tetrazol-5-yl-methylamino	698.4
A3	Me	Sulfonylmethylamino	710.3
A4	Me	N-[(3-nitrophenyl)sulfonyl]-glycinamide	858.3
A5	Me	N-(methylsulfonyl)glycinamide	751.4
A6	Me	N-[(phenylmethyl)sulfonyl]-glycinamide	825.4
A7	Me	N-(phenylsulfonyl)glycinamide	813.4
A8	Me	N-[(trifluoromethyl)sulfonyl]-glycinamide	805.4
A9	Me	N-[(2-nitrophenyl)-sulfonyl]glycinamide	858.1
A10	Me	N-[(4-nitrophenyl)sulfonyl]-glycinamide	858.3
A11	Me	N-[(4-fluorophenyl)sulfonyl]-glycinamide	831.4
A12	Me	N-[(3-fluorophenyl)sulfonyl]-glycinamide	831.4
A13	Me	N-[(2-fluorophenyl)sulfonyl]-glycinamide	831.5
A14	Me	N-[(4-chlorophenyl)sulfonyl]-glycinamide	848.3
A15	Me	N-[(3-chlorophenyl)sulfonyl]-glycinamide	848.4
A16	Me	N-[[4-(thionitroso)phenyl]sulfonyl]glycinamide	870.6
A17	Me	N-[[4-[(trifluoromethyl)sulfonyl]-phenyl]-sulfonyl]glycinamide	946.1
A18	Me	N-[[4-(trifluoromethyl)-phenyl]-sulfonyl]-glycinamide	881.8
A19	Me	N-[(4-cyanophenyl)sulfonyl]-glycinamide	839.0
A20	Me	N-[(3-chloro-4-methylphenyl)-sulfonyl]-glycinamide	862.3
A21	Me	N-[[4-chloro-3-nitrophenyl]-sulfonyl]-glycinamide	893.4
A22	Me	N-[(3,5-dichlorophenyl)sulfonyl]-glycinamide	882.9
A23	Me	N-[(4-methyl-3-nitrophenyl)sulfonyl]-glycinamide	873.1
A24	Me	N-[[2-chloro-5-(trifluoromethyl)-phenyl]-sulfonyl]glycinamide	916.5
A25	Me	N-[(5-carboxy-2-chlorophenyl)sulfonyl]-glycinamide	892.3
A26	Me	N-[(2,5-dichlorophenyl)-sulfonyl]-glycinamide	879.5
A27	Me	N-[(3,4-difluorophenyl)-sulfonyl]-glycinamide	849.6
A28	Me	N-[(3,5-dichloro-2-hydroxyphenyl)-sulfonyl]-glycinamide	895.5
A29	Me	N-[(2,4,5-trichlorophenyl)sulfonyl]glycinamide	913.3 (M-1) -
A30	Me	N-[(5-carboxy-4-chloro-2-fluorophenyl)-sulfonyl]glycinamide	910.6 (M-1) -
A31	Me	N-[[5-(dimethylamino)-1-naphthalenyl]-sulfonyl]-glycinamide	907.3
A32	Me	N-(2-naphthalenylsulfonyl)-glycinamide	864.2
A33	Me	N-[(4-(phenyl)phenyl)sulfonyl]glycinamide	889.5
A34	Me	N-[(6-ethoxy-2-benzothiazolyl)-sulfonyl]-glycinamide	915.2

A35	Me	N-[[2-chloro-5-[[ (phenylmethyl)-amino]-carbonyl]phenyl]-sulfonyl]glycinamide	980.6
A36	Me	N-[[2-chloro-5-[[ (2-trifluoroethyl)-amino]carbonyl]-phenyl]-sulfonyl]glycinamide	970.5 (M-1)-
A37	Me	N-[[2-chloro-5-[[ (cyclopropylmethyl) amino]-carbonyl]phenyl]sulfonyl]glycinamide	944.4
A38	Me	N-[[3-nitro-4-(2-pyrimidinylthio)-phenyl]sulfonyl]glycinamide	968.4
A39	Me	N-[[2-chloro-4-(acetyl amino)-phenyl]sulfonyl]glycinamide	902.5 (M-1)-
A40	Me	N-[[3-chloro-4-(2-benzoxazolylthio)phenyl]-sulfonyl]glycinamide	1005.5 (M-1)-
A41	Me	N-[[3,5-dichloro-4-(4-nitrophenoxy)phenyl]-sulfonyl]glycinamide	1018.5
A42	Me	N-[[5-(acetyl amino)-1,3,4-thiadiazol-2-yl]-sulfonyl]-glycinamide	878.5
A43	Me	N-[[3-cyanophenyl]-sulfonyl]-glycinamide	838.4
A44	Me	N-[[3-(aminosulfonyl)-5-chlorophenyl]-sulfonyl]glycinamide	924.4 (M-1)-
A45	Me	N-[[3,5-bis(trifluoromethyl)-phenyl]-sulfonyl]glycinamide	949.4
A46	Me	N-{4-[5-(3-(4-chlorophenyl)-3-oxo-1-propenyl)2-furanyl]-phenyl}sulfonyl glycinamide	1043.5
A47	Me	3{[benzylamino]carbonylphenyl-sulfonyl}- glycinamide	946.6
A48	Me	N-[[[[(2-trifluoroethyl)-amino]-carbonyl]phenyl]sulfonyl]-glycinamide	938.5
A49	Me	N-[[3-[(benzylamino)-sulfonyl]-5-chlorophenyl]-sulfonyl]glycinamide	1030.6
A50	CHF <sub>2</sub>	glycine	710.4
A51	CHF <sub>2</sub>	2H-tetrazol-5-yl-methylamino	734.4
A52	CHF <sub>2</sub>	N-[[3,5-dichlorophenyl]-sulfonyl]-glycinamide	918.9
A53	CHF <sub>2</sub>	N-[[3-chlorophenyl]-sulfonyl]-glycinamide	883.3
A54	CHF <sub>2</sub>	N-[[5-(acetyl amino)-1,3,4-thiadiazol-2-yl]sulfonyl]-glycinamide	914.5
A55	CHF <sub>2</sub>	N-[3-aminosulfonyl-5-chlorophenyl]sulfonyl- glycinamide	962.4
A56	CF <sub>3</sub>	2H-tetrazol-5-yl-methylamino	752.9
A57	CHF <sub>2</sub>	N-[[3-chloro-5-[[ (3,3,3-trifluoropropanoyl) amino] sulfonyl]phenyl]sulfo nyl]glycinamide	1073.4
A58	CHF <sub>2</sub>	N-[[3-chloro-5- [(hexanoylamino) sulfonyl]phenyl]sulfonyl]) glycinamide	1061.3
A59	Me	N-[[[1,1'-biphenyl]-3-ylsulfonyl] glycinamide	890.4
A60	Me	N-[[4'-methoxy[1,1'-biphenyl]-4-yl)sulfonyl] glycinamide	920.1
A61	Me	N-[[3',5'-dichloro[1,1'-biphenyl]-4- yl)sulfonyl] glycinamide	958.5
A62	CHF <sub>2</sub>	N-[[4'-chloro[1,1'-biphenyl]-3-yl)sulfonyl] glycinamide	960.6
A63	CHF <sub>2</sub>	N-{4-(2-methylphenoxy)phenyl}sulfonyl} glycinamide	956.2
A64	CHF <sub>2</sub>	N-{[3-(2-chlorophenoxy)phenyl]sulfonyl} glycinamide	976.3
A65	CHF <sub>2</sub>	OH	653.5
A66	CHF <sub>2</sub>	N-[[4'-methyl[1,1'-biphenyl]-3-yl)sulfonyl] glycinamide	940.1
A67	CHF <sub>2</sub>	N-[[3',5'-bis(trifluoromethyl)[1,1'- biphenyl]-3-yl]sulfonyl] glycinamide	1061.8
A68	CHF <sub>2</sub>	N-[[5-[(4-cyanobenzoyl) amino]-1,3,4- thiadiazol-2-yl]sulfonyl] glycinamide	1001.9

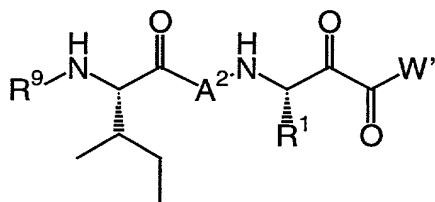
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A69	CHF <sub>2</sub>	N-((5-[(2-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl) glycineamide	1011.2
A70	CHF <sub>2</sub>	N-((5-[(4-methoxybenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl) glycineamide	1006.8
A71	CHF <sub>2</sub>	N-((5-[(3-methoxybenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl) glycineamide	1007.1
A72	CHF <sub>2</sub>	N-((5-[(3,5-dimethylbenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl) glycineamide	1004.8
A73	CHF <sub>2</sub>	N-[(3-phenoxyphenyl)sulfonyl] glycineamide	941.8
A74	Me	OH	617.4
A75	CHF <sub>2</sub>	N-((5-[(3-methylbutanoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl) glycineamide	957.0
A76	CHF <sub>2</sub>	N-((5-(hexanoylamino)-1,3,4-thiadiazol-2-yl)sulfonyl) glycineamide	971.0
A77	CHF <sub>2</sub>	methyloxy glycine	724.4
A78	Me	N-[(3-chloro-5-[(3-chlorobenzoyl)amino]sulfonyl) glycineamide	1066.1
A79	CHF <sub>2</sub>	N-([4'-(trifluoromethyl)[1,1'-biphenyl]-3-yl)sulfonyl) glycineamide	993.9
A80	CHF <sub>2</sub>	N-([1,1'-biphenyl]-3-ylsulfonyl) glycineamide	926.1
A81	CHF <sub>2</sub>	N-((5-[(4-tert-butylbenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl) glycineamide	1033.1
A82	CHF <sub>2</sub>	N-[(3-chloro-5-[(3-methylbutanoyl)amino]sulfonyl) phenyl)sulfonyl] glycineamide	1047.7
A83	CHF <sub>2</sub>	4-(4-methoxyphenyl)-5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl-methylamino	907.8
A84	CHF <sub>2</sub>	N-((5-[(4-ethylbenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl) glycineamide	1005.2
A85	CHF <sub>2</sub>	N-((5-[(4-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl) glycineamide	1011.5
A86	CHF <sub>2</sub>	N-((5-[(3,5-difluorobenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl) glycineamide	1013.1
A87	CHF <sub>2</sub>	N-((5-[(3-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl) glycineamide	1011.3
A88	Me	allylamino	656.4
A89	Me	propargylamino	654.5
A90	Me	t-butyloxy glycine	730.5
A91	Me	benzylamino	706.4
A92	Me	N-pyrrolidinyl	670.3
A93	Me	1,1,1-trifluoroethylamino	698.2
A94	Me	glycineamide	673.4
A95	Me	L-alanine	688.5
A96	Me	L-aspartic acid	732.4
A97	Me	homoglycine	688.5

**Table 2**



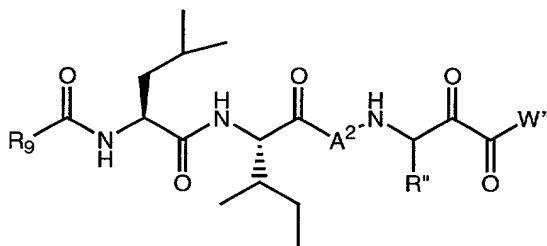
Ex #	W"	(M+1)+
B1	Tert-butyl glycine	816.4
B2	Glycine	760.3
B3	Aminomethyltetrazole	784.4
B4	Methoxyl	717.3
B5	N-[(3-chlorophenyl)-sulfonyl]-glycinamide	933.3
B6	N-[(5-carboxy-2-chlorophenyl)-sulfonyl]glycinamide	978.2
B7	N-[[5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl]-glycinamide	982.5 (M+1+H <sub>2</sub> O)+
B8	N-[(3,5-dichlorophenyl)-sulfonyl]-glycinamide	967.6
B9	N-[(4-methyl-3-nitrophenyl)-sulfonyl]glycinamide	958.4
B10	N-[(3-carboxyl-4-chloro-2-fluorophenyl)sulfonyl]-glycinamide	995.4
B11	N-[[3-chloro-4-(acetylamino)-phenyl]sulfonyl]glycinamide	1116.5
B12	N-[(3-[(benzoylamino)sulfonyl]-5-chlorophenyl)sulfonyl] glycinamide	1117.4
B13	Glycine t-Butylester	788.9
B14	N-[(3-chloro-4-methylphenyl)sulfonyl] glycinamide	948.3
B15	N-[(5-[(3-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl] glycinamide	1061.3
B16	Glycine methylester	774.6
B17	N-[(2,4-dichloro-5-methylphenyl)sulfonyl] glycinamide	982.6
B18	N-[(3,4-difluorophenyl)sulfonyl] glycinamide	935.7
B19	N-[(3,4-dichlorophenyl)sulfonyl] glycinamide	1026.7
B20	N-[[4-(3,5-dimethyl-1-piperidinyl)-3-nitrophenyl]sulfonyl] glycinamide	1056.0
B21	N-[(3-nitrophenyl) sulfonyl] glycinamide	944.8
B22	N-[[5-(hexanoylamino)-1,3,4-thiadiazol-2-yl]sulfonyl] glycinamide	1021.1
B23	N-[(2,4-dichloro-5-carboxylphenyl)sulfonyl] glycinamide	1012.6

**Table 3**

10

Ex#	R <sup>9</sup>	A <sup>2</sup>	R <sup>1</sup>	W"	(M+1) +
C1	4-chlorophenyl-2-furanylcarbonyl	Cha	Et	glycine	659.4

C2	4-chlorophenyl-2-furanylcarbonyl	Cha	Et	N-(trifluoromethyl-sulfonyl)-glycinamide	790.3
C3	4-chlorophenyl-2-furanylcarbonyl	Cha	Et	N-(3,5-dichlorophenyl-sulfonyl)-glycinamide	866.6
C4	4-chlorophenyl-2-furanylcarbonyl	Cha	Et	N-(3-nitrophenyl-sulfonyl)glycinamide	841.3
C5	4-chlorophenyl-2-furanylcarbonyl	HyPOBn	CH <sub>2</sub> CHF <sub>2</sub>	aminomethyl tetrazole	769.3
C6	[(9-oxo-9H-fluoren-1-yl)carbonyl	HyPOBn	CH <sub>2</sub> CHF <sub>2</sub>	2H-tetrazol-5-yl-methylamino-	771.5
C7	[(9-oxo-9H-fluoren-1-yl)carbonyl	HyPOBn	CH <sub>2</sub> CHF <sub>2</sub>	Gly(OtBu)	803.4
C8	[(9-oxo-9H-fluoren-1-yl)carbonyl	HyPOBn	CH <sub>2</sub> CHF <sub>2</sub>	Glycine	747.3
C9	[(9-oxo-9H-fluoren-1-yl)carbonyl	HyPOBn	CH <sub>2</sub> CHF <sub>2</sub>	N-([5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl)glycinamide	951.2
C10	[(9-oxo-9H-fluoren-1-yl)carbonyl	HyPOBn	CH <sub>2</sub> CHF <sub>2</sub>	N-([5-(hexanoylamino)-1,3,4-thiadiazol-2-yl]sulfonyl)glycinamide	1007.9
C11	[(9-oxo-9H-fluoren-1-yl)carbonyl	HyPOBn	CH <sub>2</sub> CHF <sub>2</sub>	N-([5-[(4-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl]sulfonyl)glycinamide	1048.3
C12	[(9-oxo-9H-fluoren-1-yl)carbonyl	HyPOBn	CH <sub>2</sub> CHF <sub>2</sub>	N-([5-[(4-ethylbenzoyl)amino]-1,3,4-thiadiazol-2-yl]sulfonyl)glycinamide	1041.8
C13	[(9-oxo-9H-fluoren-1-yl)carbonyl	HyPOBn	CH <sub>2</sub> CHF <sub>2</sub>	Gly(OtBu)	801.9
C14	[(9-oxo-9H-fluoren-1-yl)carbonyl	HyPOBn	CH <sub>2</sub> CHF <sub>2</sub>	Glycine	746.0
C15	[(9-oxo-9H-fluoren-1-yl)carbonyl	HyPOBn	CH <sub>2</sub> CHF <sub>2</sub>	N-([5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl)glycinamide	950.1
C16	[(9-oxo-9H-fluoren-1-yl)carbonyl	HyPOBn	CH <sub>2</sub> CHF <sub>2</sub>	N-([5-[(3-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl]sulfonyl)glycinamide	1046.7
C17	[(9-oxo-9H-fluoren-1-yl)carbonyl	HyPOBn	CH <sub>2</sub> CHF <sub>2</sub>	N-([1,1'-biphenyl]-3-ylsulfonyl)glycinamide	961.2

**Table 4**

EX#	R <sup>9</sup>	A <sup>2</sup>	R''	W''	(M+1) +
D1	Pyrazine carbonyl	Cha	allyl	allylamino	668.3
D2	3,3-diphenyl propionyl	Cha	allyl	allylamino	770.9
D3	Acetyl	Cha	allyl	allylamino	604.1
D4	2-pyridine carbonyl	Cha	allyl	allylamino	667.4
D5	3-pyridine carbonyl	Cha	allyl	allylamino	667.4
D6	4-nitropyrazole carbonyl	Cha	allyl	allylamino	701.5
D7	2-carboxyl benzoyl	Cha	allyl	allylamino	710.3
D8	3-pyridine carbonyl	Cha	ehtyl	allylamino	655.4
D9	3,3-diphenyl propionyl	Cha	ethyl	allylamino	758.8
D10	Pyrazine carbonyl	Octahydro indazole 2-carboxylic acid	ethyl	glycine	672.4
D11	Pyrazine carbonyl	Octahydro indazole 2-carboxylic acid	ethyl	Glycine t-butylester	728.5
D12	3,3-diphenyl propionyl	Cha	ethyl	hydroxyl	719.6

10           The following Table 5 contains representative examples envisioned by the present invention. At the start of each table is one formula followed by species **Z1** through **Z67** demonstrating the intended substitution of Z; species **1a** through **1bw** demonstrating the intended substitution of R<sup>1</sup>;

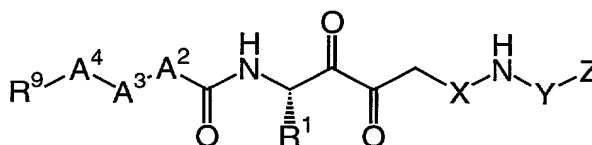
15   and species **9a** through **9n** demonstrating the intended substitution of R<sup>9</sup>. Each entry in each table is intended to be paired with each formula at the start of the table. For example, Example 100 in Table 5 is intended to be paired with each of formulae **Z1**, **Z2**, **Z3**, **Z4**, ... through

20   **Z67** of Table 4, as well as each of formulae **1a**, **1b**, **1c**, **1d**,

5 ... through **1bw** of Table 4, as well as each of formulae **9a**,  
**9b**, **9c**, **9d**, ... through **9n** of Table 4; thereby representing  
Example 100-9a-1a-Z1, 100-9a-1a-Z2, 100-9a-1a-Z3, ...  
through 243-9n-1bw-Z67.

As an illustration, Example 100-9a-1a-Z1 is N-(2-  
10 pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-  
2-oxo-3-aminopentanoyl-N-(methylsulfonyl) glycinamide.

**Table 5**



Z is selected from:

<b>Z1:</b> methyl	<b>Z21:</b> ethyl
<b>Z2:</b> propyl	<b>Z22:</b> trifluoromethyl
<b>Z3:</b> phenyl	<b>Z23:</b> benzyl
<b>Z4:</b> 4-phenyl-phenyl	<b>Z24:</b> 4-NCS-phenyl
<b>Z5:</b> 2-fluorophenyl-	<b>Z25:</b> 3-fluorophenyl-
<b>Z6:</b> 4-fluorophenyl-	<b>Z26:</b> 2-chlorophenyl-
<b>Z7:</b> 3-chlorophenyl-	<b>Z27:</b> 4-chlorophenyl-
<b>Z8:</b> 2-cyanophenyl-	<b>Z28:</b> 3-cyanophenyl-
<b>Z9:</b> 4-cyanophenyl-	<b>Z29:</b> 2-nitrophenyl-
<b>Z10:</b> 3-nitrophenyl-	<b>Z30:</b> 4-nitrophenyl-
<b>Z11:</b> 2-CF <sub>3</sub> SO <sub>2</sub> -phenyl-	<b>Z31:</b> 3-CF <sub>3</sub> SO <sub>2</sub> -phenyl-
<b>Z12:</b> 4-CF <sub>3</sub> SO <sub>2</sub> -phenyl-	<b>Z32:</b> 2-CF <sub>3</sub> -phenyl-
<b>Z13:</b> 3-CF <sub>3</sub> -phenyl-	<b>Z33:</b> 4-CF <sub>3</sub> -phenyl-
<b>Z14:</b> 3-NO <sub>2</sub> -4-Cl-phenyl-	<b>Z34:</b> 3-Cl-4-CH <sub>3</sub> -phenyl-
<b>Z15:</b> 2-Cl-5-CF <sub>3</sub> -phenyl-	<b>Z35:</b> 2-Cl-5-CO <sub>2</sub> H-phenyl-
<b>Z16:</b> 3-NO <sub>2</sub> -4-CH <sub>3</sub> -phenyl-	<b>Z36:</b> 3-Cl-5-NH <sub>2</sub> SO <sub>2</sub> -phenyl-
<b>Z17:</b> 3,5-diCF <sub>3</sub> -phenyl-	<b>Z37:</b> 3,4-diCF <sub>3</sub> -phenyl-
<b>Z18:</b> 3,5-diCl-phenyl-	<b>Z38:</b> 2,5-diCl-phenyl-
<b>Z19:</b> 3,4-diCl-phenyl-	<b>Z39:</b> 3,5-diF-phenyl-
<b>Z20:</b> 2,5-diF-phenyl-	<b>Z40:</b> 3,4-diF-phenyl-
<b>Z41:</b> 2-F-4-Cl-5-CO <sub>2</sub> H-phenyl-	
<b>Z42:</b> 2,4-diCl-5-CO <sub>2</sub> H-phenyl-	
<b>Z43:</b> 2,4-diCl-5-CH <sub>3</sub> CO <sub>2</sub> -phenyl-	
<b>Z44:</b> 2,4-diCl-5-CH <sub>3</sub> -phenyl-	
<b>Z45:</b> 2-OH-3,5-diCl-phenyl-	
<b>Z46:</b> 2,4,5-triCl-phenyl-	
<b>Z47:</b> 3,5-diCl-4-(4-NO <sub>2</sub> phenyl)phenyl-	
<b>Z48:</b> 2-Cl-5-benzyl-NHCO-phenyl-	
<b>Z49:</b> 2-Cl-5-CF <sub>3</sub> CH <sub>2</sub> -NHCO-phenyl-	
<b>Z50:</b> 2-Cl-5-cyclopropylmethyl-NHCO-phenyl-	
<b>Z51:</b> 2-Cl-4-CH <sub>3</sub> CONH-phenyl-	
<b>Z52:</b> 5-CH <sub>3</sub> CONH-1H-pyrrol-2-yl-	
<b>Z53:</b> 5-phenylCONH-furan-2-yl-	
<b>Z54:</b> 2-CH <sub>3</sub> CONH-2,3-dihydrofuran-5-yl-	

**Z55:** 3-Cl-5-(phenylCONHSO<sub>2</sub>)-phenyl-  
**Z56:** 3-Cl-5-CH<sub>3</sub>CONH-phenyl-  
**Z57:** 5-ethoxy-benzothiazol-2-yl  
**Z58:** naphth-2-yl  
**Z59:** (CH<sub>3</sub>CONH) thiadiazolyl-  
**Z60:** (s-butyl-CONH)-thiadiazolyl-  
**Z61:** (n-pentyl-CONH) thiadiazolyl-  
**Z62:** (phenyl-CONH)-thiadiazolyl-  
**Z63:** (3-Cl-phenyl-CONH) thiadiazolyl-  
**Z64:** (benzoxazol-2-yl)-  
**Z65:** (1H-benzimidazol-2-yl)-  
**Z66:** thiazolo[4,5-c]pyrid-2-yl-  
**Z67:** 9H-purin-8-yl

5

R<sup>1</sup> is selected from:

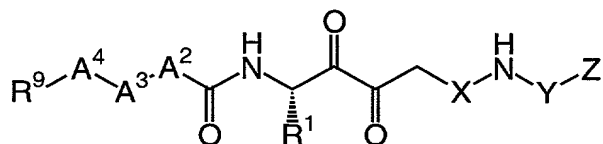
<b>1a:</b> -CH <sub>2</sub> CH <sub>3</sub>	<b>1ah:</b> -CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> C(CH <sub>3</sub> ) <sub>3</sub>
<b>1b:</b> -CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	<b>1ai:</b> -CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>
<b>1c:</b> -CH(CH <sub>3</sub> ) <sub>2</sub>	<b>1aj:</b> -CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>
<b>1d:</b> -CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	<b>1ak:</b> -CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>
<b>1e:</b> -CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	<b>1al:</b> -CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>
<b>1f:</b> -CH <sub>2</sub> C(CH <sub>3</sub> ) <sub>3</sub>	<b>1am:</b> -CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>
<b>1g:</b> -CH <sub>2</sub> CH <sub>2</sub> C(CH <sub>3</sub> ) <sub>3</sub>	<b>1an:</b> -CH <sub>2</sub> CHF <sub>2</sub>
<b>1h:</b> -CH <sub>2</sub> CF <sub>3</sub>	<b>1ao:</b> -CH <sub>2</sub> CH <sub>2</sub> CHF <sub>2</sub>
<b>1i:</b> -CH <sub>2</sub> CH <sub>2</sub> CF <sub>3</sub>	<b>1ap:</b> -CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CHF <sub>2</sub>
<b>1j:</b> -CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CF <sub>3</sub>	<b>1aq:</b> -CH=CH <sub>2</sub>
<b>1k:</b> -CH <sub>2</sub> CH=CH <sub>2</sub>	<b>1ar:</b> -CH=CHCH <sub>3</sub>
<b>1l:</b> cis-CH <sub>2</sub> CH=CH(CH <sub>3</sub> )	<b>1as:</b> trans-CH <sub>2</sub> CH=CH(CH <sub>3</sub> )
<b>1m:</b> -CH <sub>2</sub> CH <sub>2</sub> CH=CH	<b>1at:</b> -CH <sub>2</sub> CH=C(CH <sub>3</sub> ) <sub>2</sub>
<b>1n:</b> -CH <sub>2</sub> CH <sub>2</sub> CH=C(CH <sub>3</sub> ) <sub>2</sub>	<b>1au:</b> phenyl
<b>1o:</b> benzyl	<b>1av:</b> phenethyl
<b>1p:</b> phenpropyl	<b>1aw:</b> phenbutyl
<b>1q:</b> -CH <sub>2</sub> CO <sub>2</sub> H	<b>1ax:</b> -CH <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> H
<b>1r:</b> -CH <sub>2</sub> CO <sub>2</sub> C(CH <sub>3</sub> ) <sub>3</sub>	<b>1ay:</b> -CH <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> C(CH <sub>3</sub> ) <sub>3</sub>
<b>1s:</b> -CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> NH <sub>2</sub>	<b>1az:</b> (naphth-2-yl)ethyl-
<b>1t:</b> (cyclobutyl)methyl-	<b>1ba:</b> (cyclobutyl)ethyl-
<b>1u:</b> (cyclobutyl)propyl-	<b>1bb:</b> cyclopropyl
<b>1v:</b> cyclobutyl	<b>1bc:</b> cyclopentyl
<b>1w:</b> cyclohexyl	<b>1bd:</b> (4-ethylphenyl)ethyl-
<b>1x:</b> (2-methylphenyl)ethyl-	<b>1be:</b> (4-i-propylphenyl)ethyl-
<b>1y:</b> (3-methylphenyl)ethyl-	<b>1bf:</b> (4-t-butylphenyl)ethyl-
<b>1z:</b> (4-methylphenyl)ethyl-	<b>1bg:</b> (4-hydroxyphenyl)ethyl-
<b>1aa:</b> (2-fluorophenyl)ethyl-	<b>1bh:</b> (2-chlorophenyl)ethyl-
<b>1ab:</b> (3-fluorophenyl)ethyl-	<b>1bi:</b> (3-chlorophenyl)ethyl-
<b>1ac:</b> (4-fluorophenyl)ethyl-	<b>1bj:</b> (4-chlorophenyl)ethyl-
<b>1ad:</b> (2-bromophenyl)ethyl-	<b>1bk:</b> (3-bromophenyl)ethyl-
<b>1ae:</b> (4-bromophenyl)ethyl-	<b>1bm:</b> (4-phenoxy-phenyl)ethyl-
<b>1af:</b> (4-phenyl-phenyl)ethyl-	<b>1bn:</b> (2,5-dimethylphenyl)ethyl-
<b>1ag:</b> (2,4-dimethylphenyl)ethyl-	<b>1bo:</b> (2,6-difluorophenyl)ethyl-
<b>1bp:</b> (4-cyclohexyl-phenyl)ethyl-	
<b>1bq:</b> (4-cyclopentyl-phenyl)ethyl-	
<b>1br:</b> (4-cyclobutyl-phenyl)ethyl-	
<b>1bs:</b> (4-cyclopropyl-phenyl)ethyl-	
<b>1bt:</b> (2-trifluoromethylphenyl)ethyl-	
<b>1bu:</b> (3-trifluoromethylphenyl)ethyl-	
<b>1bv:</b> (4-trifluoromethylphenyl)ethyl-	
<b>1bw:</b> (2,3,4,5,6-pentafluorophenyl)ethyl-	



5 R<sup>9</sup> is selected from:

- 9a:** 2-pyrazinyl-CO-  
**9b:** 4-(N-pyrrolyl)phenyl-CO-  
**9c:** 5-(4-Cl-phenyl)furan-2-yl-CO-  
**9d:** 1-anthracenyl-CO-  
**9e:** 7-NO<sub>2</sub>-anthracen-1-yl-CO-  
**9f:** (3-phenyl-2-cyanomethoxyphenyl)-CO-  
**9g:** 5-(2-Cl-3-CF<sub>3</sub>-phenyl)-furan-2-yl-CO-  
**9h:** 5-(4-Cl-phenyl)-furan-2-yl-CO-  
**9i:** 5-(pyrid-2-yl)-thiophen-2-yl-CO-  
**9j:** (2-CH<sub>3</sub>O-phenyl)ethyl-CO-  
**9k:** (3-benzopyrrolyl)ethyl-CO-  
**9l:** (N-phenyl-5-propyl-imidazol-4-yl)-CO-  
**9m:** 1-naphthyl-SO<sub>2</sub>-  
**9n:** 5-(isoxazol-2-yl)-thiophen-2-yl-SO<sub>2</sub>-

Table 5 (cont.)



Ex#	R <sup>9</sup>	A <sup>4</sup>	A <sup>3</sup>	A <sup>2</sup>	R <sup>1</sup>	X	Y	Z
100	9a - 9n	Ile	Leu	Cha	1a - 1bw	-(C=O)-	-SO <sub>2</sub> -	Z1 - Z67
101	9a - 9n	Val	Leu	Cha	1a - 1bw	-(C=O)-	-SO <sub>2</sub> -	Z1 - Z67
102	9a - 9n	Dpa	Leu	Cha	1a - 1bw	-(C=O)-	-SO <sub>2</sub> -	Z1 - Z67
103	9a - 9n	Ile	Val	Cha	1a - 1bw	-(C=O)-	-SO <sub>2</sub> -	Z1 - Z67
104	9a - 9n	Val	Val	Cha	1a - 1bw	-(C=O)-	-SO <sub>2</sub> -	Z1 - Z67
105	9a - 9n	Dpa	Val	Cha	1a - 1bw	-(C=O)-	-SO <sub>2</sub> -	Z1 - Z67
106	9a - 9n	Ile	Glu	Cha	1a - 1bw	-(C=O)-	-SO <sub>2</sub> -	Z1 - Z67
107	9a - 9n	Val	Glu	Cha	1a - 1bw	-(C=O)-	-SO <sub>2</sub> -	Z1 - Z67
108	9a - 9n	Dpa	Glu	Cha	1a - 1bw	-(C=O)-	-SO <sub>2</sub> -	Z1 - Z67
109	9a - 9n	Ile	Leu	Hyp	1a - 1bw	-(C=O)-	-SO <sub>2</sub> -	Z1 - Z67
110	9a - 9n	Val	Leu	Hyp	1a - 1bw	-(C=O)-	-SO <sub>2</sub> -	Z1 - Z67
111	9a - 9n	Dpa	Leu	Hyp	1a - 1bw	-(C=O)-	-SO <sub>2</sub> -	Z1 - Z67
112	9a - 9n	Ile	Val	Hyp	1a - 1bw	-(C=O)-	-SO <sub>2</sub> -	Z1 - Z67
113	9a - 9n	Val	Val	Hyp	1a - 1bw	-(C=O)-	-SO <sub>2</sub> -	Z1 - Z67
114	9a - 9n	Dpa	Val	Hyp	1a - 1bw	-(C=O)-	-SO <sub>2</sub> -	Z1 - Z67
115	9a - 9n	Ile	Glu	Hyp	1a - 1bw	-(C=O)-	-SO <sub>2</sub> -	Z1 - Z67
116	9a - 9n	Val	Glu	Hyp	1a - 1bw	-(C=O)-	-SO <sub>2</sub> -	Z1 - Z67
117	9a - 9n	Dpa	Glu	Hyp	1a - 1bw	-(C=O)-	-SO <sub>2</sub> -	Z1 - Z67
118	9a - 9n	Ile	Leu	Pro	1a - 1bw	-(C=O)-	-SO <sub>2</sub> -	Z1 - Z67
119	9a - 9n	Val	Leu	Pro	1a - 1bw	-(C=O)-	-SO <sub>2</sub> -	Z1 - Z67
120	9a - 9n	Dpa	Leu	Pro	1a - 1bw	-(C=O)-	-SO <sub>2</sub> -	Z1 - Z67
121	9a - 9n	Ile	Val	Pro	1a - 1bw	-(C=O)-	-SO <sub>2</sub> -	Z1 - Z67
122	9a - 9n	Val	Val	Pro	1a - 1bw	-(C=O)-	-SO <sub>2</sub> -	Z1 - Z67
123	9a - 9n	Dpa	Val	Pro	1a - 1bw	-(C=O)-	-SO <sub>2</sub> -	Z1 - Z67
124	9a - 9n	Ile	Glu	Pro	1a - 1bw	-(C=O)-	-SO <sub>2</sub> -	Z1 - Z67
125	9a - 9n	Val	Glu	Pro	1a - 1bw	-(C=O)-	-SO <sub>2</sub> -	Z1 - Z67
126	9a - 9n	Dpa	Glu	Pro	1a - 1bw	-(C=O)-	-SO <sub>2</sub> -	Z1 - Z67
127	9a - 9n	bond	Leu	Cha	1a - 1bw	-(C=O)-	-SO <sub>2</sub> -	Z1 - Z67
128	9a - 9n	bond	Val	Cha	1a - 1bw	-(C=O)-	-SO <sub>2</sub> -	Z1 - Z67
129	9a - 9n	bond	Glu	Cha	1a - 1bw	-(C=O)-	-SO <sub>2</sub> -	Z1 - Z67





The compounds of Formula (I) are expected to inhibit the activity of Hepatitis C Virus NS3 protease. The NS3 protease inhibition is demonstrated using assays for NS3 protease activity, for example, using the assay described below for assaying inhibitors of NS3 protease. The compounds of Formula (I) are expected to show activity against NS3 protease in cells, as demonstrated by the cellular assay described below. Thus, the compounds of Formula (I) are potentially useful in the cure and prevention of HCV infections.

#### Expression and Purification of NS3 Protease

The plasmid cf1SODp600, containing the complete coding region of HCV NS3 protease, genotype 1a, was obtained from ATCC (database accession: DNA Seq. Acc. M62321, originally deposited by Chiron Corporation). PCR primers were designed that allow amplification of the DNA fragment encoding the NS3 protease catalytic domain (amino acids 1 to 192) as well as its two N-terminal fusions, a 5 amino acid leader sequence MGAQH (serving as a expression tag) and a 15 amino acid His tag MRGSHHHHHMGAQH. The NS3 protease constructs were cloned in the bacterial expression vector under the control of the T7 promoter and transformed in *E. coli* BL 21 (DE3) cells. Expression of the NS3 protease was obtained by addition of 1 mM IPTG and cells were growing for additional 3h at 25°C. The NS3 protease constructs have several fold difference in expression level, but exhibit the same level of solubility and enzyme specific activity. A typical 10 L fermentation yielded approximately 200 g of wet cell paste. The cell paste was stored at -80°C. The NS3 protease was purified based on published procedures (Steinkuhler C. et al. *Journal of Virology* 70, 6694-6700, 1996 and Steinkuhler C. et al. *Journal of Biological Chemistry* 271, 6367-6373, 1996.) with some modifications. Briefly, the cells were resuspended in lysis buffer (10 mL/g) containing PBS buffer (20 mM sodium phosphate, pH 7.4, 140 mM NaCl), 50%

5 glycerol, 10 mM DTT, 2% CHAPS and 1mM PMSF. Cell lysis was performed with use of microfluidizer. After homogenizing, DNase was added to a final concentration 70 U/mL and cell lysate was incubated at 4°C for 20 min. After centrifugation at 18,000 rpm for 30 min at 4°C supernatant  
10 was applied on SP Sepharose column (Pharmacia), previously equilibrated at a flow rate 3 mL/min in buffer A (PBS buffer, 10% glycerol, 3 mM DTT). The column was extensively washed with buffer A and the protease was eluted by applying 25 column volumes of a linear 0.14 - 1.0 M NaCl  
15 gradient. NS3 containing fractions were pooled and concentrated on an Amicon stirred ultrafiltration cell using a YM-10 membrane. The enzyme was further purified on 26/60 Superdex 75 column (Pharmacia), equilibrated in buffer A. The sample was loaded at a flow rate 1 mL/min,  
20 the column was then washed with a buffer A at a flow rate 2 mL/min. Finally, the NS3 protease containing fractions were applied on Mono S 10/10 column (Pharmacia) equilibrated in 50 mM Tris.HCl buffer, pH 7.5, 10% glycerol and 1 mM DTT and operating at flow rate 2 mL/min. Enzyme was eluted by  
25 applying 20 column volumes of a linear 0.1 - 0.5 M NaCl gradient. Based on SDS-PAGE analysis as well as HPLC analysis and active site titration, the purity of the HCV NS3 1a protease was greater than 95%. The enzyme was stored at -70°C and diluted just prior to use.

30

#### Enzyme Assays

Concentrations of protease were determined in the absence of NS4a by using the peptide ester substrate Ac-DED(Edans)EEAbuψ[COO]ASK(Dabcyl)-NH<sub>2</sub> (Taliani et al. *Anal. Biochem.* 240, 60-67, 1996.) and the inhibitor, H-Asp-Glu-Val-Val-Pro-boroAlg-OH and the inhibitor, H-Asp-Glu-Val-Val-Pro-boroAlg-OH and by using tight binding reaction conditions (Bieth, *Methods Enzymol.* 248, 59-85, 1995). Best data was obtained for an enzyme level of 50 nM.  
40 Alternately, protease (63 µg/ml) was allowed to react with 3 µM NS4a, 0.10 mM Ac-Glu-Glu-Ala-Cys-pNA, and varying

5 level of H-Asp-Glu-Val-Val-Pro-boroAla-OH (0-6  $\mu\text{M}$ ).

Concentrations of protease were determined from linear plots of Activity vs. [inhibitor]. Molar concentrations of proteases were determined from the x-intercept.

$K_m$  values were determined measuring the rate of  
10 hydrolysis of the ester substrate over a range of concentrations from 5.0 to 100  $\mu\text{M}$  in the presence of 3  $\mu\text{M}$  KKNS4a (KKGSVVIVGRIVLSGKPAIIPKK). Assays were run at 25°C, by incubating ~1 nM enzyme with NS4a for 5 min in 148  $\mu\text{l}$  of buffer (50 mM Tris buffer, pH 7.0, 50% glycerol, 2% Chaps, 15 and 5.0 mM DTT. Substrate (2.0  $\mu\text{l}$ ) in buffer was added and the reaction was allowed to proceed for 15 min. Reactions were quenched by adding 3.0  $\mu\text{L}$  of 10% TFA, and the levels of hydrolysis were determined by HPLC. Aliquots (50  $\mu\text{L}$ )  
20 were injected on the HPLC and linear gradients from 90% water, 10% acetonitrile and 0.10 % TFA to 10% water, 90% acetonitrile and 0.10% TFA were run at a flow rate of 1.0 mL/min over a period of 30 min. HPLCs were run on a HP1090 using a Rainin 4.6 x 250 mm C18 column (cat # 83-201-C) fluorescent detection using 350 and 500 nm as excitation  
25 and emission wavelengths, respectively. Levels of hydrolysis were determined by measuring the area of the fluorescent peak at 5.3 min. 100% hydrolysis of a 5.0  $\mu\text{M}$  sample gave an area of  $7.95 \pm 0.38$  fluorescence units.). Kinetic constants were determined from the iterative fit of  
30 the Michaelis equation to the data. Results are consistent with data from Liveweaver Burk fits and data collected for the 12.8 min peak measured at 520 nm.

Enzyme activity was also measured by measuring the increase in fluorescence with time by exciting at 355 nm  
35 and measuring emission at 495 nm using a Perkin Elmer LS 50 spectrometer. A substrate level of 5.0  $\mu\text{M}$  was used for all fluorogenic assays run on the spectrometer.

5 Inhibitor Evaluation *In vitro*

Inhibitor effectiveness was determined by measuring enzyme activity both in the presence and absence of inhibitor. Velocities were fit to the equation for competitive inhibition for individual reactions of inhibitors with the enzyme using

$$v_i / v_o = [K_m (1 + I/K_i) + S] / [K_m + S].$$

The ratio  $v_i / v_o$  is equal to the ratio of the Michaelis equations for velocities measured in the presence ( $v_i$ ) and absence ( $v_o$ ) of inhibitor. Values of  $v_i / v_o$  were measured over a range of inhibitor concentrations with the aid of an Excel™ Spreadsheet. Reported  $K_i$  values are the average of 3-5 separate determinations. Under the conditions of this assay, the  $IC_{50}$  and  $K_i$ s are comparable measures of inhibitor effectiveness.

Using the methodology described above, compounds of the present invention were found to exhibit  $K_i$ 's of  $\leq 60 \mu M$ , thereby confirming the utility of the compounds of the present invention as effective NS3 protease inhibitors. Preferred compounds of the present invention have  $K_i$ 's of  $\leq 1 \mu M$ . More preferred compounds of the present invention have  $K_i$ 's of  $\leq 100$  nM. Most preferred compounds of the present invention have  $K_i$ 's of  $\leq 10$  nM.

Inhibitor Evaluation in Cell Assay.

The following method was devised to assess inhibitory action of test compounds on the HCV NS3 protease in cultured cells. Because it is not possible to efficiently infect cells with hepatitis C virus, an assay was developed based on co-expression in transfected cell lines of two plasmids, one is able to direct synthesis of the NS3 protease and the other to provide a polypeptide analogous to a part of the HCV non-structural protein containing a single known peptide sequence highly susceptible to cleavage by the protease. When installed in cultured cells by one of a variety of standard methods, the substrate plasmid produces a stable polypeptide of approximately

5 50KD, but when the plasmid coding for the viral protease is  
co-expressed, the enzymatic action of the protease  
hydrolyzes the substrate at a unique sequence between a  
cysteine and a serine pair, yielding products which can be  
detected by antibody-based technology, eg, a western blot.  
10 Quantitation of the amounts of precursor and products can  
be done by scanning film auto-radiograms of the blots or  
direct luminescence-based emissions from the blots in a  
commercial scanning device. The general organization of the  
two plasmids is provided in Scheme 6. The coding sequences  
15 for the NS3 protease and the substrate were taken from  
genotype 1a of HCV, but other genotypes, eg 2a, may be  
substituted with similar results.

The DNA plasmids are introduced into cultured cells  
using electroporation, liposomes or other means. Synthesis  
20 of the protease and the substrate begin shortly after  
introduction and may be detected within a few hours by  
immunological means. Therefore, test compounds are added at  
desired concentrations to the cells within a few minutes  
after introducing the plasmids. The cells are then placed  
25 in a standard CO<sub>2</sub> incubator at 37°C, in tissue culture  
medium eg Dulbecco-modified MEM containing 10% bovine  
serum. After 6-48 hours, the cells are collected by  
physically scraping them from plastic dishes in which they  
have been growing, centrifuging them and then lysing about  
30 10<sup>6</sup> of the concentrated cells in a minimal volume of  
buffered detergent, eg 20 µl of 1% sodium dodecyl sulfate  
in 0.10 M Tris-HCl, pH 6.5, containing 1% mercaptaethanol  
and 7% glycerol. The samples are then loaded onto a  
standard SDS polyacrylamide gel, the polypeptides separated  
35 by electrophoresis, and the gel contents then  
electroblotted onto nitrocellulose or other suitable paper  
support, and the substrate and products detected by  
decoration with specific antibodies.

Although this invention has been described with  
40 respect to specific embodiments, the details of these  
embodiments are not to be construed as limitations. Various



5 equivalents, changes and modifications may be made without departing from the spirit and scope of this invention, and it is understood that such equivalent embodiments are part of this invention.

10 Preparation of H-Asp-Glu-Val-Val-Pro-boroAlg pinanediol ester•trifluoroacetate

Preparation of Boc-Asp(O<sup>t</sup>Bu)-Glu(O<sup>t</sup>Bu)-Val-Val-Pro-OH.

Boc-Val-Pro-OBzl was prepared by dissolving H-Pro-OBzl (20  
15 g, 83 mmol) in 50 mL of chloroform and adding Boc-Val-OH  
(18.0 g, 83 mmol), HOBt (23.0g, 165 mmol), NMM (9.0 mL, 83  
mmol) and DCC (17.0 g, 83 mmol). The reaction mixture was  
stirred overnight at room temperature. The mixture was  
filtered and solvent was evaporated. Ethyl acetate was  
20 added and insoluble material was removed by filtration.  
The filtrate was washed with 0.2N HCl, 5% NaHCO<sub>3</sub>, and  
saturated aqueous NaCl. It was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered  
and evaporate to give a white solid (30 g, 75 mmol, 90%).  
ESI/MS calculated for C<sub>22</sub>H<sub>32</sub>N<sub>2</sub>O<sub>5</sub> +H: 405.2. Found 405.6.

25 Boc-Val-Val-Pro-OBzl was prepared by dissolving Boc-Val-  
Pro-OBzl (14.0 g, 35.0 mmol) in 4N HCl in dioxane (20 mL)  
and allowing the reaction to stir for 2h under an inert  
atmosphere at room temperature. The reaction mixture was  
30 concentrated by evaporation *in vacuo* and ether was added to  
yield a precipitate. It was collected by filtration under  
nitrogen. After drying *in vacuo* with P<sub>2</sub>O<sub>5</sub>, H-Val-Pro-OBzl  
was obtained as a white solid (22.6 g, 30.3 mmol, 89%).  
(ESI/MS calculated for C<sub>17</sub>H<sub>24</sub>N<sub>2</sub>O<sub>3</sub> +H: 305.2. Found:

35 305.2.) H-Val-Pro-OBzl (9.2 g, 27 mmol) was dissolved in  
50 mL of CH<sub>2</sub>Cl<sub>2</sub> and Boc-Val-OH (7.3 g, 27 mmol), HOBt (7.3  
g, 54 mmol), NMM (3.0 mL, 27 mmol) and DCC (5.6 g, 27 mmol)  
were added. The reaction mixture stirred overnight at room  
temperature. The mixture was filtered and the filtrate was  
40 evaporated. The residue was dissolved in ethyl acetate and  
the solution was re-filtered. The filtrate was washed with

5 0.2N HCl, 5% NaHCO<sub>3</sub>, and saturated aqueous NaCl. It was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to give a yellow oil (10.6 g, 21.1 mmol, 78%). ESI/MS calculated for C<sub>27</sub>H<sub>41</sub>N<sub>3</sub>O<sub>6</sub> + Na: 526.3 Found: 526.4.

10 Z-Glu(O<sup>t</sup>Bu)-Val-Val-Pro-OBzl was also prepared by DCC coupling. H-Val-Val-Pro-OBzl·hydrochloride was obtained in a 100% yield by treating the corresponding Boc compound with anhydrous HCl using the procedure described for H-Val-Pro-OBzl (ESI/MS calculated for C<sub>22</sub>H<sub>33</sub>N<sub>3</sub>O<sub>4</sub> + H: 404.2.

15 Found 404.3.). The amine hydrochloride (7.40 g, 16.8 mmol) was dissolved in 185 mL DMF and 25 mL THF. Z-Glu(O<sup>t</sup>Bu)-OH (5.60 g, 16.8 mmol), HOBt (4.60 g, 33.6 mmol), NMM (1.85 mL, 16.8 mmol) and DCC (3.5 g, 16.8 mmol) were added. The reaction was run and the product was isolated by the

20 procedure described for Boc-Val-Val-Pro-OBzl. The tetrapeptide was obtained as a white foam (12.0 g, 16.1 mmol, 96%). ESI/MS calculated for C<sub>39</sub>H<sub>54</sub>N<sub>4</sub>O<sub>9</sub> + Na: 745.4. Found: 745.4.

25 H-Glu(O<sup>t</sup>Bu)-Val-Val-Pro-OH was prepared by dissolving Z-Glu(O<sup>t</sup>Bu)-Val-Val-Pro-OBzl (2.90 g, 3.89 mmol) in 100 mL methanol containing 1% acetic acid. Pearlman's catalyst, Pd(OH)<sub>2</sub>, (100mg) was added and the flask was placed on the Parr hydrogenation apparatus with an initial H<sub>2</sub> pressure of

30 34 psi. After three hours, the catalyst was removed by filtration through a celite pad and the filtrate was evaporated *in vacuo* to yield a yellow oil (1.30 g, 2.61 mmol, 67%). ESI/MS calculated for C<sub>24</sub>H<sub>42</sub>N<sub>4</sub>O<sub>7</sub> +H: 499.3 Found: 499.4.

35

Boc-Asp(O<sup>t</sup>Bu)-Glu(O<sup>t</sup>Bu)-Val-Val-Pro-OH was prepared by active ester coupling. Boc-Asp(O<sup>t</sup>Bu)-N-hydroxysuccinimide ester was prepared by coupling Boc-Asp(O<sup>t</sup>Bu)-OH (3.00 g, 10.4 mmol) to N-hydroxysuccinimide (1.19 g, 10.4 mmol) in

40 50 mL of ethylene glycol dimethyl ether. The reaction flask was placed in an ice bath at 0°C and DCC was added.

5 The reaction mixture was slowly allowed to warm to room temperature and to stir overnight. The mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was dissolved in ethyl acetate and re-filtered. The filtrate was evaporated give a white solid.

10 Recrystallized from ethyl acetate: hexane gave the activated ester (3.38 g, 8.80 mmol, 84%). (ESI/MS calculated for  $C_{17}H_{26}N_2O_8 + H$ : 387.2. Found: 387.4.) H-Glu(O<sup>t</sup>Bu)-Val-Val-Pro-OH (5.40 g, 10.8 mmol) was dissolved in 100 mL of water. Sodium bicarbonate (0.92 g, 11.0 mmol)

15 was added followed by triethylamine (2.30 mL, 16.5 mmol). The N-hydroxysuccinimide ester (3.84 g, 10.0 mmol) was dissolved in 100 mL dioxane and was added to the H-Glu(O<sup>t</sup>Bu)-Val-Val-Pro-OH solution. The mixture stirred overnight at room temperature. Dioxane was removed *in*

20 *vacuo* and 1.0 M HCl was added to give pH ~ 1. The product was extracted into ethyl acetate. The ethyl acetate solution was washed with 0.2 N HCl, dried over sodium sulfate, filtered, and evaporated to yield a yellow oil (7.7 g, 10.0 mmol, 100%). ESI/MS calculated for  $C_{37}H_{63}N_5O_{12}$

25 + Na: 792.4. Found: 792.4.

Boc-Asp(O<sup>t</sup>Bu)-Glu(O<sup>t</sup>Bu)-Val-Val-Pro-boroAlg-pinandediol was prepared by coupling the protected pentapeptide to H-boroAlg-pinandediol. Boc-Asp(O<sup>t</sup>Bu)-Glu(O<sup>t</sup>Bu)-Val-Val-Pro-OH

30 (1.8 g, 2.3 mmol) was dissolved 10 mL THF and was cooled to -20°C. Isobutyl chloroformate (0.30 mL, 2.3 mmol) and NMM (0.25 mL, 2.3 mmol) were added. After 5 minutes, this mixture was added to H-boroAlg-pinandediol (0.67 g, 2.3 mmol) dissolved in THF (8 mL) at -20°C. Cold THF (~5 mL)

35 was used to aid in the transfer. Triethylamine (0.32 mL, 2.3 mmol) was added and the reaction mixture was allowed to come to room temperature and to stir overnight. The mixture was filtered and solvent was removed by evaporation. The residue was dissolved in ethyl acetate,

40 washed with 0.2 N HCl, 5% NaHCO<sub>3</sub>, and saturated NaCl. The organic phase was dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and

5 evaporated to yield a yellow oil. Half of the crude  
product (1.5 g) was purified in 250 mg lots by HPLC using a  
4 cm x 30 cm Rainin C-18 reverse phase column. A gradient  
from 60: 40 acetonitrile: water to 100% acetonitrile was  
run over a period of 28 minutes at a flow rate of 40  
10 mL/min. The fractions containing the desired product were  
pooled and lyophilized to yield a white solid (46 mg). <sup>1</sup>H-  
NMR (CD<sub>3</sub>OD) δ 0.9-1.0 (m, 15H), 1.28 (s, 3H), 1.3 (s, 3H),  
1.44 (3s, 27H), 1.6-2.8 (20H), 3.7(m, 1H), 3.9(m, 1H), 4.1-  
4.7 (7H), 5.05(m, 2H), 5.9(m, 1H). High res (ESI/MS)  
15 calculated for C<sub>51</sub>H<sub>86</sub>N<sub>6</sub>O<sub>13</sub>B<sub>1</sub> +H: 1001.635. Found 1001.633.

Preparation of H-Asp-Glu-Val-Val-Pro-boroAlg pinanediol  
ester•trifluoroacetate: The hexapeptide analog, Boc-  
Asp(O<sup>t</sup>Bu)-Glu(O<sup>t</sup>Bu)-Val-Val-Pro-boroAlg-pinanediol, (22.5  
20 mg, 0.023 mmol) was treated with 2 mL of TFA: CH<sub>2</sub>Cl<sub>2</sub> (1: 1)  
for 2 h. The material was concentrated *in vacuo* and  
purified by HPLC using C-18 Vydac reverse phase (2.2 x 25  
cm) column with a gradient starting at 60:40  
acetonitrile/water with 0.1%TFA going to 95:5 over 25  
25 minutes with a flow rate of 8 mL/min. The product eluted  
at 80% acetonitrile. The fractions were evaporated and  
dried under high vacuum to give 8.9 mg (49%) of the desired  
product as white amorphous solid. <sup>1</sup>H-NMR (CD<sub>3</sub>OD) δ 5.82  
(m, 1H), 5.02 (m, 2H), 4.58(m, 1H), 4.42 (m, 3H), 4.18 (m,  
30 4H), 3.90 (m, 1H), 3.62 (m, 1H), 3.01 (dd, 1H), 2.78 (m,  
1H), 2.62 (m, 1H), 2.41-1.78 (m, 17H), 1.31 (s, 3H), 1.28  
(s, 3H), 1.10 - 0.82 (m, 15H). ESI/MS calculated for  
C<sub>38</sub>H<sub>62</sub>N<sub>6</sub>O<sub>11</sub>B +H: 789.2. Found: 789.2.